Rare Diseases Report 2019

WHITEPAPER: RARE DISEASES IN MALAYSIA

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IDEAS
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Foreword

Rare diseases are characterised by their low prevalence, the majority of them are chronically debilitating and life threatening. Due to their rare condition, there is a lack of experience in managing rare diseases in the local community. In 2018, the Institute for Democracy and Economic Affairs (IDEAS) embarked on a research and advocacy project on rare disease in Malaysia to improve the welfare of these patients.

As an organisation that believes in individual liberty and responsibility, we believe that every Malaysian must have sufficient knowledge to exercise their choices. In addition to addressing the information challenge, we have advocated for a policy framework that ensures accessibility of treatment, by providing avenues for assistance to be channelled, and incentives where possible.

We have undertaken concerted efforts to create a platform that would facilitate an inclusive discussion on the challenges surrounding rare diseases in Malaysia. We started the project by forming a national working group which consists of five reputed experts in the field. The working group has evolved as the main platform for deliberation during this project. Over the course of eighteen months, IDEAS also successfully built strong relationships with patient groups, industry members, healthcare professionals and government officials involved in the rare disease agenda. We have been very encouraged by the response from the Ministry of Health and have always found them forthcoming. We are also honoured to share the difficult journey undertaken by the patient advocacy groups. These multi-stakeholder relationships were further harnessed through consultations to understand the multiple perspectives involved in progressing the rare disease agenda. This diversity of perspectives has added immense value to developing the depth of our understanding on rare disease in Malaysia and has allowed us to initiate a comprehensive policy discussion for the country.

Bearing in mind, the complexity of issues involved in this discussion due to both fiscal constraints and diversity of clinical needs, creative solutions are needed. We commissioned a whitepaper to examine these challenges and provide practical solutions for the consideration of the government. Written by Professor Dr. Thong Meow Keong and Dr. Azlina Ahmad Annuar from University Malaya, with the support of IDEAS research team including Laurence Todd, Wan Ya Shin and Vaisnavi Rao, this whitepaper is a humble attempt at outlining some solutions to improve the welfare of individuals with rare diseases in Malaysia. This paper was further reviewed by Dr. Asrul Akmal, Dr. Keng Wee Teik and Dr. Ngu Lock Hock, esteemed members of the working group. We thank the private sector, government, members of the working group and most importantly patient advocacy groups for their continuous support throughout this project and hope that this whitepaper will pave the way for further progress in this area. We will appreciate any feedback not only to improve the whitepaper but also to make our efforts to improve the policy environment around rare diseases more effective and inclusive.

Ali Salman
CEO of IDEAS

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The authors would like to thank IDEAS for their support in raising the profile of rare diseases in the country and their tireless efforts in arranging consultations with the various stakeholders, including within the various governmental ministries, insurance companies, industry and patient support groups. Input from the representatives from the various stakeholders was very crucial and helped us refine areas to focus on and highlight issues with the existing systems. We are indebted to the individuals and families affected by rare disorders for sharing their stories, and their challenges remain as reminders of how much still needs to be done. We thank the Malaysian Rare Disorders Society for generously allowing us to utilise some of their survey findings to provide quantitative data to illustrate the unmet needs of this community. Insightful comments and expertise from the working group members and other professionals in various multi-disciplinary teams had also been invaluable in enhancing this Whitepaper, and we thank them for their ongoing contributions to supporting the needs of the rare disease community. Finally, we thank the University of Malaya staff and our families for their support.

Executive Summary

by Thong Meow Keong And Azlina Ahmad Annuar

This whitepaper was commissioned to investigate the current situation of rare diseases in Malaysia. Due to the perceived rarity of such conditions, the rare disease community was often marginalized, and the lack of a holistic policy on rare diseases impacted how these diseases were managed. These developments resulted in early mortality and severe morbidity, including the learning and physical handicapping of patients with rare diseases. In short, rare diseases remain underdiagnosed, underfunded and face many unmet needs Although some steps were taken to address these issues, including the provision of funding for drugs for selected conditions over the last few years, more needs to be done to match the pace of how these diseases are managed in regional countries and global rare disease community to ensure equity in healthcare. Through extensive consultations with various stakeholders and surveys of patient groups and their families, this whitepaper addresses key areas that need to be reviewed to improve not only the healthcare mechanism but also social, ethical, legal and financial management as well as the governance framework for Rare Disease (RD.)

At present, there is no clear definition of RD in Malaysia, and there is no RD registry in the country to accurately determine the number of patients affected by these disorders. An RD registry would enable more accurate estimates of the epidemiology and inform actuarial calculations as well as appropriate allocation of healthcare resources for RD. A national policy on rare diseases would allow clearer designation of duties and responsibilities of various governmental ministries and agencies to coordinate efforts into better care and services for the RD community.

Malaysia requires more emphasis on RDs and continuous professional development programs of the medical community are in urgent need of a revamp to improve the awareness of RDs amongst medical practitioners. Moreover, there is a need the capacity-building in the healthcare sector to cater for the increasing number of patients and the complications involved. Decentralization of these services is necessary and regional centres for RDs are recommended. The lack of preventive programs for RDs, in particular population screening, such as maternal and newborn screening for RDs and prenatal diagnostic services, has resulted in persistence of high birth prevalence of RD, thus resulting in a lack of improvement in infant mortality rates in Malaysia for

the past 15 years. In addition, the lack of clinical geneticists and allied healthcare professionals like genetic counsellors, laboratory technologists, dietitians, speech and occupational therapists further impacts the quality of care that these patients deserve. Social services such as specific interventions and early education programs, enhancement of teachers' education in RDs and timely and sufficient welfare services are vital. The compartmentalization of healthcare and social care working in their 'silos' across the various governmental ministries has meant a lack of effective coordination amongst them, which created gaps, duplications and redundancies and wastages and, at the same time, led to feelings of frustration and deprivation of services by the RD community.

Patients and their families often also face challenges with education and career opportunities. This whitepaper outlines several suggestions on how children with debilitating conditions can be supported to receive better education, including allocations to schools for more awareness campaigns to teachers and students, as well as funding to improve infrastructure to enable access for those with disabilities.

Furthermore, there is also a need for the establishment of a RD and Orphan Drug Act to better assess available medicine and particularly to evaluate treatments that are expensive. Without protection from legislations, RD patients have encountered ad-hoc allocation of medical care that could be life-saving. This whitepaper, outlines the current situation of access to drugs and the funding structure , and several economic models are proposed as possible avenues that government agencies could look into. Governmental non-compliance to international and national conventions – for example, not allocating resources for universal healthcare and education or protection of child's rights by providing timely and effective medicines for RDs – is a serious problem which must be addressed.

In summary, this whitepaper aims to highlight several key areas that need to be addressed urgently. A number of proposals are well within the capability of the governmental agencies, corporate companies, public and industry to look into the existing policies and examine how those could be improved based on what has been outlined here. Others may require more careful analysis and forward planning. However, given the rapid advancement in biomedical science in developing treatments, decisive action needs to be taken urgently to improve the quality of life for the RD community.

"No country can claim to have achieved universal healthcare if it has not adequately and equitably met the needs of those with rare diseases."

Helen Clark, the former prime minister of New Zealand and headed the United Nations Development Program (2017)

Introduction

A. Context of the publication

1. To inform about the current rare disease situation in Malaysia

2. To highlight the lack of a formal definition of rare diseases or policy and the impact this has on various areas of the management of the diseases

3. To outline areas that are currently being addressed and to identify gaps in the medical care received by the affected individuals in order to suggest improvements

4. To propose economic models for financing orphan drugs and other treatments

B. List of participants in the Working Groups

Professor Dr Thong Meow Keong (consultant paediatrician, clinical geneticist)
Associate Professor Dr Azlina Ahmad Annuar (geneticist)
Associate Professor Dr Asrul Akaml Shafie (pharmacoeconomist)

Keng Wee Teik (clinical geneticist)
Ngu Lock Hock (clinical geneticist)

C. Definition and rare diseases as non-communicable diseases

The World Health Organization (WHO) defines a rare disease, also known as orphan disease, as any disease which affects a small percentage of the general population. Although individually rare, collectively there are over 6,000 types and this constitutes a large number of patients, who share many issues in common (EURORDIS, 2009). About 80% of rare diseases are genetic in nature. However, those that are caused by other factors such as exposure to environmental factors, chemicals during pregnancy, infections and rare cancers are not inherited.

Examples of rare diseases include inherited metabolic diseases such as lysosomal storage diseases; neuromuscular diseases such as Duchenne muscular dystrophy and spinal muscular atrophy; blood diseases such as haemophilia; bone disorders such as brittle bone disease and achondroplasia; and adult-onset diseases such as Huntington's disease and motor neurone disease.

Rare disease patients in Europe are represented by the European Organisation for Rare Diseases (EURORDIS), a non-governmental patient-driven alliance of over 761 rare disease patient organisations in 68 countries. EURORDIS defines rare diseases as those affecting less than five people in 10,000 of the general population (EURORDIS, 2009). Meanwhile, the United States of America (USA) defines a disease as rare if it affects less than 200,000 persons out of the total population (Field et al., 2010). In Taiwan, rare diseases are acknowledged not in terms of their prevalence but by their inclusion in the Rare Disease registry by name (Hsu et al 2018).

In Malaysia, there is no official definition thus far as to what is regarded as a rare disease. As the first step to providing a definition for local families, the Malaysian Rare Disorders Society (MRDS) has decided upon a classification on the basis of prevalence – that is, one in every 4,000 people of the general population. Having an official and accurate definition is paramount to addressing a multitude of issues faced by families living with rare diseases in Malaysia. For example, not having a clear definition leads to many issues with indifference from policy makers, inadequate healthcare provisions and restricted access to crucial life-changing medication.

In 2016, the Malaysian Ministry of Health (MOH) published a report titled "National Strategic Planning for Non-Communicable Diseases (NCDs) 2016-2025", which focused on lifestyle risk factors such as hypertension, obesity, cancer and hypercholesterolemia, as well as control of tobacco use, salt and alcohol consumption (Ministry of Health Malaysia, 2016). Indeed, there was no data on NCDs for segments of the population below 15 years old nor strategic planning for control and treatment needed for rare diseases in Malaysia.

D. Historical aspects of rare diseases

The existence of 'rare diseases' were known in ancient history. Usually these conditions, often congenital malformations or rare disorders, attracted attention due to their appearance or engendered negative perception and stigmatization based on the idea that they occurred due to unexplained or superstitious causes. With the advent of genetic and genomic sequencing technology, the molecular bases of thousands of rare diseases were elucidated. The term rare diseases, in the plural form and without any further details, appeared in the United States in the mid-1970s and was stabilised in the Orphan Drug Act of 1984. Huyard (2009) argued in her socio-historical inquiry that this category – which appeared initially as a by-product of the orphan drug issue in the United States of America – is a boundary object. As such, it has different specific local uses: a 'meaningless' category for physicians while relating to the patients' experience of illness.

E. Statistics and epidemiology of rare diseases

Between 300 and 400 million people worldwide live with rare diseases (IFPMA 2014) which are defined in the European Union as diseases affecting not more than five people in 10,000. Half of those affected are children, and 30% die before the age of 5 years. (National Institutes of Health 2019) Although individual diseases will typically affect small populations, the total number of people living with rare diseases amounts to approximately 4% of the global population. Therefore it is conservatively estimated there are 1.2 million people affected by RD in Malaysia. Another paper reported about 9% – or 45 million people – in South East Asia are afflicted by orphan diseases (Right diagnosis, 2015). As most rare diseases are complex, chronic, degenerative and frequently life-threatening, access to affordable, good quality and physically accessible health care and services, including long-term care, is essential. (RD International 2019) With treatment options available for only 5% of rare diseases, they are largely neglected; market and public policy failures account in considerable measure for this. (UN Economic and Social council 2019)

F. Recent global developments within the rare disease community

Patients with rare diseases and their affected families face many challenges. As these conditions are often debilitating and chronic, they pose considerable long term psychological, medical and financial burden on the patient as well as their parents, siblings and extended family. (Department of Health UK 2013)

Walker et al. also calculated the impact of rare diseases on the health-care system in Western Australia; hospital stays related to rare disease were, on average, approximately 3 days longer than stays for the general population (Walker et al., 2016). In 2010, cohort members who were alive represented approximately 2% of the Western Australian population. The cohort accounted for 4.6% of people discharged from hospital and 9.9% of hospital discharges, and it had a greater average length of stay than the general population. The total cost of hospital discharges for the cohort represented 10.5% of 2010 state inpatient hospital costs. These results affirm previous findings. For example, Yoon et al. reported that in a pediatric population from two states in the United States comprising patients with hospital codes for birth defects and genetic diseases, the cohort represented approximately 2.5% of the population; yet they accounted for 9 to 12% of pediatric hospital admissions and 16 to 28% of total costs (Yoon et al., 1997). Another recent study showed that pediatric inpatients with diagnostic codes linked to genetic disease have a significant and disproportionate impact on resources and costs in the US health-care system (Gonzaludo et al., 2019).

The United Nations High Commissioner for Human Rights (2019) outlined some of the key human rights challenges of extending universal health coverage, such as access to medicines, deficits in the health work force and the very sizeable populations and groups who have been excluded from health coverage. It concluded that universal health coverage must be an inclusive right, encompassing service delivery, and incorporate effective access and other determinants of health, as well as formal coverage.

Many developed countries had formulated National Rare Disease policies. For example, Rare Voices Australia (RVA) launched the report, *Disability & Rare Disease: Towards Person Centred Care for Australians with Rare Diseases (2019)* and with the development of the National Strategic Action Plan for Rare Diseases (the Action Plan), they had broadened the scope to include disability issue with a National Disability Insurance Scheme (NDIS). The Action Plan is a comprehensive, collaborative and evidence-based approach to achieving the best possible health and wellbeing outcomes for Australians living with rare disease. It is based on three key principles: person-centred, equity of access and sustainable systems and workforce.

This will expand on RVA's previous work - *Call for a National Rare Disease Framework: 6 Strategic Priorities and it will also align with the APEC Action Plan on Rare Diseases.* The Action Plan has 3 core Pillars, with each Pillar outlining Priorities, Actions and Implementation. The Pillars are: 1. Awareness and Education 2. Care and Support and 3. Research and Data. (Rare Voices Australia 2017) (APEC 2018)

The current situation in Malaysia today

A. The need for accurate data on rare diseases in Malaysia

Rare diseases tend to draw the short straw in the current climate of competing healthcare resources. As they are presumed to only affect a very small number of Malaysians and are considered as non-communicable diseases, little attention is paid to them and there is limited data, if any, on their prevalence and burden in Malaysia.

In addition, Malaysia currently spends only 4.2% of GDP on healthcare as of 2018. Therefore, there is an urgent need to address the shortcomings of the national strategy particularly the lack of funding in healthcare services. Proper acknowledgement of rare diseases, beginning with an official definition and recognition as a national healthcare issue, will help to garner more attention towards these conditions in addition to providing support for the patients and families. Although rare diseases are characterised by their low prevalence individually, in reality these conditions collectively impact the lives of a large number of Malaysians as patients and carers are faced with financial, psychological and social burden. Many who suffer from rare diseases often feel isolated, uncared for and vulnerable. Being properly recognised as a serious healthcare matter and making rare diseases an inclusive issue will help to garner more awareness and respect for these individuals.

B. Definition of RD in Malaysia

Currently there is no standardized definition for RD in Malaysia. It is recommended that the definition is guided by the disease prevalence (Kaplan et al., 2013; Shafie et al., 2016) It was suggested to use the prevalence of 1 in 4,000 in Malaysia as accepted by MRDS as the original aim was the need to focus on rare diseases not currently covered by government support. Currently certain rare diseases have received governmental funding such as screening of secondary 4 students for thalassaemia trait and treatment of beta thalassaemia major patients (1 in 2,500) as well as newborn cord blood screening for congenital hypothyroidism (1 in 3,000). Patients with Down syndrome received educational support from non-governmental organisations such as Kiwanis and eligible for registration as 'Persons with Disabilities'' by the Malaysian government. There is also a national thalassaemia registry. Hence on the basis of needs, priority is on other rare diseases and the prevalence of 1 in 4,000 was empirical adopted. It was also reasoned that once an equal level playing field is achieved i.e. healthcare support is provided for all diseases, the prevalence of 1 in 2,000 for RDs may be used in concert with international norms.

If definition by prevalence is used, this will facilitate pharmaceutical registration for the disease, and give a uniform definition for the whole country. The disadvantage is the prevalence of these rare conditions will depend on prevalence established in developed countries, usually Western countries which may not reflect the true prevalence in Malaysia. Be that as it may, until the true prevalence of each RD is known from a local Malaysian registry, this will be an acceptable pathway.

Registry for rare diseases

In developed countries, RD registries were typically established through public funding. Currently there is no official registry for RDs in Malaysia. Registries require a sustainable source of funding, usually public or

governmental funding over long term. Hospital personnel such as medical doctors, research officers or trained nurses may be required to report rare diseases or sentinel conditions. In addition, it will require clerical support staff or an online reporting system. Thus, in some countries, there are also legislations which make it compulsory to report the cases, similar to what is done for infectious diseases in Malaysia.

Secondly, it needs to use the up-to-date classification system (Thong, 2018). Currently the govt uses the ICD-10 classification for patient's diagnosis on discharge. It is acknowledged that ICD-10 has limitations in classification of rare diseases. ICD-11 was used in many countries. It is recommended that Malaysian government gradually switched to ICD-11 classification as this will require training and changes in the system. There are some limitations with ICD-11 as it will record hospital discharges but not outpatient or ambulatory patient services. Therefore the use of ICD-11 is only a stop gap measure.

Alternatively, discharge data may be extracted for inpatients and subjected to analysis for RD disease prevalence using ICD-11 codes. This subset of data will facilitate faster availability of data and epidemiology of RD in Malaysia.

Why the need for accurate data from registry?

Accurate data will inform resource allocation for diagnosis, treatment, prevention, rehabilitation and public educational program towards RD. It will also provide evidence of the need for research and training of the medical and allied health staff members on the needs of RD community. It will inform the development of laboratory services, and the relevant expertise required.

Moreover, accurate data will facilitate sound actuarial analysis and provided information for insurance industry to provide coverage for rare diseases and congenital disorders which are currently exclude from any insurance cover and reimbursements. Through consultations with representatives from insurance companies for insight for this white paper, it was apparent that whilst insurance companies may be willing to explore alternative models of insurance to cover rare disease patients, the lack of data regarding several key aspects of medical care hampers an accurate assessment on their part. In particular, uncertainties about clear diagnosis and complex treatments unnerves the insurance companies, and the representatives voiced the need for more data on the likely cost of treatments required over the lifespan of patients. Some of this uncertainty could be overcome if more research was invested into understanding rare diseases so that some of these issues pertaining to clinical course of the diseases and treatments can be addressed. However, it must be stated that the sentiment of insurance companies that any rare disease, regardless of the cost of treatment – even if it was minimal – would still be excluded from any policies should be revised. The strict criteria adopted by the companies may be incorrectly justified, and discussions between scientists, specialists and insurance companies should be more actively encouraged so that the true clinical course of these diseases and their cost of treatment can be more accurately represented, and thus offer a fairer chance for the rare disease community to receive adequate coverage (Min et al., 2019).

Data mining of these curated statistical data on the population will facilitate actuarial calculations that will be invaluable for insurance industry to develop products and improve disease coverage. Hence population healthcare data which are de-identified or anonymised are needed to enable a more accurate calculation on healthcare resources needed for rare diseases. The government will potentially benefit economically from the accurate data as the government may licensed the use of de-identified data by various industries

The models used in the analytics of RD epidemiology will spur the development of local artificial intelligence and software industry under Industrial Revolution (IR) 4.0 for big data collection, transmission and analysis. It will spur the development of Clinical Support Decision systems used in genomic medicine as well expertise in bioinformatics and data managing.

C. Education and awareness programs

i. Medical curricula and healthcare professionals

In most medical schools in Malaysia, the curriculum does not include a comprehensive overview of basic genetics beyond outlining the Mendelian modes of inheritance in biochemistry courses in the first or second year. The topic of rare diseases which include many uncommon diseases and minutiae is often presented in a summarized format and incorporated into sub-curricula such as genetics, biomedical science, biochemistry and physiology and so on. For clinical training, patients with rare diseases may be used for clinical examination, usually to assess the trainee's ability to take a good history, recognize dysmorphic features and other physical findings. Physical examination during the clinical years are focused on the ability of trainees to detect and describe signs and make a provisional diagnosis. Basic investigations and management may be done but overall, it is expected patients with rare diseases are referred to tertiary centres for further investigations, counselling and management. As the medical doctors are trained to function at the level of a general medical practitioner and primary healthcare provider, hence in-depth knowledge of rare diseases is not usually required.

Medical students are then only exposed to various genetic disorders when they begin their rotation, and these are typically encountered in the paediatric wards. While it is understandable that emphasis is given to common genetic disorders like Down Syndrome, thalassaemia and G6PD deficiency, the risk of not exposing the medical students to rare disorders means that they are the frontline professionals who may mis-diagnose these disorders and delay potentially life-threatening treatment. For postgraduate education and training, only certain specialties such as paediatrics and obstetrics have a focus on rare diseases. Paediatricians and obstetricians are often the front-line specialties to be consulted when a patient with rare disease is suspected. In recent years, the training of primary care medicine specialist and other subspecialities such as oncology, surgery and neurology have also increased their teaching on rare diseases, usually in the form of genetic education. Overall, the emphasis on rare diseases is minimal as the focus is on general medicine and common diseases.

In 2011, the genetic causes for 40% out of the 7,000 types of RD have been resolved, which is a massive leap from just 2% in 1999 (Wolyniak et al., 2015). Thus, the pace of scientific advancement in genetics must be taken into consideration in the medical curricula and with new technologies with implications for treatment increasing, the knowledge of medical students in these areas needs to be improved. It must be implemented in a systematic manner to prevent gaps in knowledge to prepare them for what lies in the horizons for treatment options when dealing with genetic disorders in the future.

In 2013, the Association of Professors of Human and Medical Genetics (APHMG) recommended the application certain guidelines on medical genetics education for medical students (Hyland et al., 2013) adopted from the American Association of Medical Colleges and Howard Hughes Medical Institute report on 'Scientific Foundations for Future Physicians' 2009. Specifically, they emphasised on knowledge competency by developing basic and applied empirical skills in genetics rather than the traditional memorization-route of understanding these diseases. The comprehensive APHMG curricula also includes guidelines on the decision-making process when ordering molecular tests, using analysis tools such as

bioinformatics to decipher the information, management of symptoms and referrals to specialists. In addition, APHMG further expands on improving communication skills related to genetics, and in understanding the ethical, legal and social implications. The Ministry of Education should impose the formal inclusion of this curricula in the Malaysian medical schools in order to equip future healthcare professionals with the skills they will need in this rapidly growing field of biomedicine. Implementation of these genetics topics could be through a separate parallel track to enhance genomic education (Dhar et al., 2012) or an e-learning based curriculum as described in Metcalf et al., for genetic testing and counselling guidelines (Metcalf et al., 2012).

Universities and medical schools should also strive to increase the knowledge of the students' genetics skills on an individual basis, by offering research opportunities as well as case-based virtual labs. In turn, this would positively engage medical students into pursuing a career as clinical geneticists, which is a human resource greatly lacking in Malaysia. One recommendation is for special grants for this purpose to be offered. Due to the crowded medical curriculum, it is unlikely in the near future that rare diseases will receive further allocation of time and teaching in the medical curricula and training in all the medical schools. Thus, a centre of excellence in rare diseases or an institute for rare disorders will be required to be established in Malaysia for the purpose of training, education and research in the field of rare diseases in Malaysia. Therefore, there could be two levels of medical training for rare diseases – one for the general practitioner and genetic nurses, and the second for expertise in genetics such as clinical geneticists and allied health profession such as genetic counsellors. It is estimated that a minimum of two clinical geneticists are needed per 1 million population.

In addition, regional centres for rare diseases, ideally as part of regional genetic services are recommended for all the major regions, i.e. centre, northern, southern, eastern peninsular Malaysia and also centres in Sabah and Sarawak. Hence, additional planning for allocation of funding, training and sustainable management of these centres are required.

ii. Lay public and media: roles and responsibility

Awareness campaigns by patient support groups play an important role in helping the public understand about the symptoms and challenges faced. In this regard, over that last 10 years there has been a noticeable increase in the efforts by the patient support groups. For example, this year alone, there were multiple high level public events to raise awareness about RD. The Malaysian Rare Disorders Society were invited to commemorate World Rare Disease Day 2019 at the Kuala Lumpur City Hall, car-free morning in February 2019, attended by the Federal Territory Minister and thousands of participants. In addition, the Run for Rare event organized by the Malaysian Lysosomal Disorder Association and Sunway Medical centre was officiated by the Minister of Health and well received by the public. In addition, there were many newspaper articles, radio and television interviews featuring patients with RD, aimed towards raising the profile of these disorders.

Persons living with genetic disorders have also become much more willing to share their stories on social media platforms. This is an important shift in how information about RD is shared with the public as the patients themselves are the curators of content, and do not need to rely on media networks as they would have to do previously. By doing this, the public have gained much more meaningful insight into the daily challenges they face, how they live and enabled the patients to showcase any talents like in art, music or sports.

Preliminary data on the perception of the Malaysian public on rare diseases indicated that in general, Malaysian do not discriminate against people affected by RD but there was still some stigma attached to families as more than 60% felt that society would treat them differently if they had a family member with an RD (Samulong et al.; personal communication). Furthermore, the majority of respondents would hesitate to marry someone with a family history of genetic disorders. This level of stigma and isolation only further serves to make the RD community feel discriminated against. Also seen was a general reluctance of employers to offer jobs to those with RDs as they were perceived to require modifications to the workplace which the employers were unwilling to do. This attitude still prevails despite a governmental initiative for private companies to have 1% of their workforce comprising of disabled individuals (Khoo, Tiun, & Lee, 2013).

In the survey, a high percentage agreed that people with RDs should receive financial and medical support such as free rehabilitation, discounts for medicine, hospital fees and medical equipment (Samulong S. et al., 2019). Importantly, the public supported special allocation of funds to upgrade national schools to become more disabled-friendly with easy access and disabled toilet facilities. At the moment, there are no specific funds for this and schools often rely on parents own fundraising.

Measuring the effectiveness of these awareness campaigns qualitatively is a difficult task but recent developments in societal acceptance have been promising. For example, there is increased push for 'inclusiveness and diversity' in fashion and several RD individuals have been featured as models in campaigns including for several fashion houses and in various local fashion magazines. Governmental and corporate agencies should also explore ways to support this effort further by featuring people with RDs as models in information booklets or produce booklets specifically addressing issues concerning the RD community.

D. Investigation and management of rare diseases: clinical viewpoints

i. Diagnosis and pharmacotherapy

Currently the investigations and management of rare diseases occur in tertiary medical centres such as Hospital Kuala Lumpur and the 3 main university hospitals. This is because the diagnosis of rare diseases requires expertise in clinical genetics and knowledge of laboratory techniques. Some of these investigations are done on a research basis in universities or Institute for Medical Research and hence, for ethical reasons, the outcomes or results may not be used in the clinical practice or management of the patients. For example, laboratory research in rare diseases are performed by students in normal laboratories and not by qualified medical technologists in certified or accredited medical laboratories. Many private and public hospitals used private accredited laboratories overseas and these laboratories may require certification such CAP (College of American Pathologists certification and proficiency testing). The issue of quality control and validity of the test results are vital for the safety of the patients.

The management of patients with rare diseases requires qualified clinical geneticists or specialists with special interest in genetics. This is because the appropriate treatment, genetic counseling and long term surveillance and services must be provided to the patients and their families in a timely fashion. For example in a patient with Marfan syndrome, the clinical geneticist will need to liaise with a cardiologist regarding treatment of an aortic abnormality and the ophthalmologist regarding the lens subluxation. The doctor must also arrange cardiac screening for the parents to exclude potentially aortic and other cardiac abnormalities in one of the parents.

Many new medications and drug therapies are being approved for use in patients with rare diseases. There are over 600 orphan drugs approved by FDA for rare diseases. Hence the clinical geneticist will need to liaise with pharmacists, drug regulatory authorities and pharmacological companies for the approval, payment, transport, storage and administration of the drugs. In Malaysia, for example medications to treat lysosomal diseases are registered with and approved by the National Pharmaceutical Regulatory Agency (NPRA). This includes drugs such as enzyme replacement therapies, monoclonal antibodies and hormone replacement therapies. Many other newer drugs such as treatment for spinal muscular atrophy and Duchenne muscular dystrophy are yet to be registered in Malaysia. Again, this will require coordination between treating clinicians, patients, regulatory agencies and orphan drug companies.

Both laboratory testing in private overseas laboratories and drug therapies for some rare diseases are highly expensive and cost-prohibitive and unaffordable and not available to the majority of patients, especially those in the lower-income bracket. Some of these tests may be done in government facilities but the results may only be issued several months or even years later, if at all. Some of these diagnostic and management services are supported by the Ministry of Health of Malaysia but due to the increasing number of patients, types of genetic or genomic tests needed and high cost therapies involved, many patients are not able to access these services.

Therefore there is a need to develop genetic and genomic laboratories in various regional genetic services. Universities offering courses in biotechnology, biomedical science and similar curriculum must ensure that pathologists, scientists and laboratory technologists are competent to handle and validate genetic tests in local laboratories working in tandem with clinicians and clinical geneticists. By having a critical mass of expertise in genetic and genomic sciences will lead to development of local companies offering diagnostic and research services in Malaysia and the region. This will spur economic and job opportunities,

thus representing dividends if pro-active steps are taken to offer incubator services and capital or joint ventures with these new companies and new biotech industries.

ii. Management of non-pharmacological aspects

Non-pharmacological management of patients with rare diseases may include:

1. rehabilitation services (physiotherapy, occupational and speech therapy)
2. reproductive health services
3. supportive, medical social work and counselling services
4. dietary and nutritional support
5. palliative care
6. respite care
7. public health services to institute public awareness, education and screening programs

These services are limited in many public hospitals and in rural areas. Some such as palliative care and prenatal diagnosis are available in tertiary centres while respite care is virtually non-existent. Rehabilitation services such as speech therapy, occupational and physiotherapy are available in large public hospitals but limited in scope and numbers. These services are available in some private centres. These non-pharmacological services are independent services and funded through various Divisions and Departments within the Ministry of Health and Ministry of Education hospitals; others are funded via Ministry of Women, Family and Community Development and so on. Very little research is done in Malaysia regarding these allied health services and their roles in the management of patients with rare diseases. Support groups are limited to several active non-governmental organizations such as Malaysian Rare Disorders Society, Malaysian Lysosomal Disorders Society, and several other disease specific societies for conditions such as Apert syndrome, ichthyosis, Prader-Willi syndrome and so on. These lay NGOs organized fund-raising and disease awareness activities. Hence, overall, there is deficiency in the majority of these non-pharmacological services.

Non-medical services such as educational opportunities, institutions and vocational training for individuals with rare diseases are also in need for a detailed study and evaluation. Public amenities, facilities and services in tandem with disability services must be catered for patients with multi-system handicap and disabilities.

iii. Undiagnosed rare diseases

Many patients remain without a diagnosis despite extensive medical evaluation. The Undiagnosed Diseases Network (UDN) which is funded by the National Institutes of Health USA, was established to apply a multidisciplinary model in the evaluation of the most challenging cases and to identify the biologic characteristics of newly discovered diseases. The UDN studied 382 patients who had a complete evaluation and following extensive tests, 132 received a diagnosis, yielding a rate of diagnosis of 35%. A total of 15 diagnoses (11%) were made by clinical review alone. From this, 98 (74%) were made by exome or genome sequencing. Of the diagnoses, 21% led to recommendations regarding changes in therapy, 37% led to changes in diagnostic testing, and 36% led to variant-specific genetic counseling. The authors also successfully defined 31 new syndromes (Splinter et al 2018).

In most developing countries and in Malaysia, for the majority of patients with rare diseases, diagnosis is made after an arduous 'diagnostic odyssey' consisting of various consultations with specialists and contact

with healthcare professionals, with extensive and expensive investigations including genomic testing both in public and private centres. In the majority of the patients, diagnosis is not achieved and this group of patients has undiagnosed malformations or syndromes. It is possible that a diagnosis may be made in the future with more advanced tests. In the near term, these families live with the uncertainty of not having an accurate diagnosis. This resulted in continuing search for a diagnosis and has an impact on genetic counselling, reproductive planning and allocation of resources and in many situations, uncertainty in the prognosis and long-term management of these patients. For the patients and families, these may translate into a miserable situation and uncertain future. In many advanced countries, patients with undiagnosed rare diseases will be enrolled for research and family studies with the aim to identify the genetic basis for their conditions. In Malaysia, some recent syndromes previously not seen before in this region were identified in this manner (Thong et al., 2018b).

E. Current government practice towards rare diseases: need for collaboration and involvement of all relevant agencies and ministries

There are no specific legislations pertaining to orphan drugs in Malaysia. It was reported that challenges faced by Malaysian patients with rare diseases included delayed treatment due to late diagnosis, limited availability to genetic medicine services and expensive treatments which reduced access to these medicines. The National Medicines Policy states that there shall be appropriate procedures to enhance accessibility of orphan medicines and Ministry of Health (MOH) has prepared the Malaysian Guidelines for the Management of Orphan Drugs which will provide a framework for all stakeholders the management of orphan drugs. Issues related to the designation, regulation, marketing and procurement procedures for orphan drugs are addressed and aim to increase availability of non-commercially viable products without compromising on safety. The study stated that the major hurdle faced by MOH is on the question of affordability. The majority of orphan drugs are not listed in the MOH formulary and are procured through special approval processes.

On the 27th July 2017, the Deputy Health Minister replied in the Parliament of Malaysia that the Ministry of Health allocated a budget of MYR8.5 million annually for the treatment of 28 patients with lysosomal storage diseases with each patient needing between RM500,000 to RM1 million a year. A Technical Committee for ERT was established and a guideline on the indications and use of enzyme replacement therapy for lysosomal diseases in Malaysia was issued by the MOH in 2009. However, with the increasing number of patients and the chronic nature of these rare diseases, the funding allocated to the MOH has become insufficient. Many patients are not receiving sufficient dose for their treatment and some new patients are awaiting treatment. Unfortunately, this funding for ERT is not available in the university hospitals and patients must be referred to Hospital Kuala Lumpur Department of Genetics for further management and funding of treatment. Clearly, much more is needed to be done to improve the situation. On the 27th October 2017, Prime Minister Datuk Seri Najib Razak, in his 2018 Budget announcement said the government had also allocated a total of MYR10 million to accommodate the medical costs for rare diseases, which was on an upward trend. (NST, 27 October 2017). Prior to the 14th General Election, the Pakatan Harapan (PH) coalition issued a manifesto declaring in one of its promises (Promise 9) that it "will increase budget allocation and will provide incentives for the participation of private companies and charitable bodies to tackle rare diseases." Specific measures and actions by PH government to follow through with this promise are highly anticipated.

It was announced that allocation of MYR50mil from Budget 2019 was for the specific purpose of treating rare diseases, Hepatitis C, stunted growth among children, and providing more haemodialysis treatments and enhanced primary healthcare (EnPHC). It was later clarified that the allocation for rare diseases (mainly for enzyme replacement therapy) amounted to MYR16 million. However, in November 2019, it was reported that for 2020 Budget, funding for rare diseases was reduced from MYR16 million to MYR10 million per year. It was later clarified the sum was actually MYR16.5 million for rare diseases. On the 13th November 2019, the Deputy Minister of Health announced that the MOH has developed the National Rare Disease Framework to establish a governing committee on rare diseases in Malaysia.

Based on the above developments, there is much confusion and lack clarity on the funding mechanisms currently in Malaysia for rare diseases. There is a need for a National Policy on Rare Disease, to be inclusive in nature and incorporate investigations, management and funding of rare diseases in Malaysia to include all public hospitals and close inter-Ministerial collaboration where expertise are available for treatment of rare diseases and all relevant stakeholders. This means adequate funding for treating patients with rare diseases in university teaching hospitals must be provided to ensure that training of medical students, specialists and subspecialists as well as allied health personnel such as genetic counsellors and laboratory technologists are continued. The absence of government funding for rare diseases in university hospitals will mean that the training of future generations of medical doctors and allied health professions will be seriously jeopardised and neglected in the long-term, thus leading to harm due to late diagnosis, lack of knowledge on the treatment and not providing timely genetic counselling, prenatal diagnosis services and screening programs.

F. Review of current capabilities in government and private institutions in terms of equipment and expertise

There is limited information on the current capabilities in government and private centres. Most of the services and resources needed for patients with rare diseases are embedded into the activities and allocation of various department and agencies. Only the Malaysian Medical Council has data on the number of registered clinical geneticist and pathologists in Malaysia. There is no current official data on allied health professions although a new Act for Allied Health Professions was drafted and awaiting Parliament approval.

Some pharmacological companies have embarked on humanitarian or compassionate use of orphan drugs. These patient support schemes are limited in amount and the funding structure is complex and require detailed clinical and psychosocial assessments.

G. Current patient experiences

What is evident from the patient groups is that due to the diversity of the medical conditions, patients and their families experience a range of issues. Mis-diagnosis or delayed diagnosis and lack of access to treatment are of major concern, but so is the frustration of having many other unmet needs which are not adequately recognized.

A survey by the Malaysian Rare Disorders Society (MRDS) was conducted to understand more about experiences of living with RD in Malaysia and to determine main concerns and unmet needs. The survey concentrated on several areas, of which diagnosis, treatment, financial implications and education will be discussed here (Malaysian Rare Disorders Society, 2013). Surveys such as these give an important insight into the experiences and challenges faced by the RD community in Malaysia and at present, it represents the only report investigating this issue.

Findings from the preliminary report of 59 respondents (kindly shared by MRDS for inclusion in this whitepaper) indicates that there are several key issues that need to be addressed. Firstly, delays in diagnosis of more than 1 year was experienced by the 57% of the respondents. Whilst this may appear as a fairly low percentage but in actual fact, the journey to reach the correct diagnosis often requires consultations with as many as 3-5 doctors (36% of respondents) and 23% requiring consultations with up to 10 doctors, in a process often described as a 'diagnostic odyssey'. From our consultations with the RD families, the delays in diagnosis for the childhood onset disorders are partly due to early visits to general practitioners who attribute the symptoms as differences in 'normal' development and tell the parents not to worry, and that the children will 'catch up'. However, when the symptoms persist and appear to worsen, the parents will often be referred to specialists where the diagnosis is given within a fairly short time after that. However, families in rural areas where the lack of GPs and long distances to specialist centres experience more difficulties in this area. The respondents also reported misdiagnosis was an issue, with 19% experiencing at least one misdiagnosis.

The survey also indicated that there are various issues concerning treatment options. Almost half of respondents said there were no treatments available for their particular condition (47%). 33%who had been on treatment but stopped, reported that they were unable to continue as there was not enough money to cover the treatment or that they faced other obstacles such as no transport to get to the treatment centres or that they did not have a support system to care for other family members while they took their loved one for treatment. The same situation was true for access to recommended therapies such as occupational, speech and physiotherapy. While a large majority (69%) were able to access at least one of these therapies, the remaining 39% could not access these therapies due to the same reasons mentioned above. This underlies the inequality in treatment for the RD families and this needs to be addressed better by the ministries and agencies. With advancements in biomedical science research, newer drugs using the latest technologies including antisense oligonucleotides, recombinant gene therapies and genome editing will be available and the patient groups will be pressuring the government to approve and/or offer these drugs fully or partially subsidised.

While the loudest petitions will call for the life-saving treatments, there have also been calls for better guidelines for the management of RDs to raise the standard of care and avoid unnecessary harm to the patients. For example, the management of respiratory complications in newborns with neuromuscular disorders varies greatly between hospitals depending on how familiar the medical personnel are with the condition and in some cases, even dependent on the assertiveness of the parents in asking for more careful evaluation. This leads to great anxiety and frustration amongst the family members. Treatment of lysosomal storage disorders by enzyme replacement therapy and the 1st consensus statement for the diagnosis and management of acromegaly issues in 2019 (Malaysian Endocrine and Metabolic Society). In the case of spinal muscular atrophy (SMA), there are guidelines in place by international organisations like TREAT-NMD and the SMA care group (Mercuri et al., 2018; Finkel et al., 2019) which lists best practices for the diagnosis, rehabilitation, orthopedic and nutritional care for the patients. Similar guidelines are also available for Duchenne Muscular Dystrophy (Birnkrant et al., 2018a; 2018b). These guidelines should be widely distributed to all the hospitals and medical centres and medical personnel made aware. Patient groups should also keep abreast with the latest management options so they are able to discuss these more thoroughly with the healthcare professionals.

In terms of evaluating the financial implication of living with RD, the survey reports that 41% of the families spend up to 30% of their income on treatments for the medical condition. A third revealed that they are unable to afford the treatments, and a similar number could pay but faced financial difficulties because of the additional cost. The majority of individuals and families are absorbing the cost by using their savings, followed by seeking intermittent help from welfare organisations like zakat and charities, while others borrowed money and withdrew from their EPF accounts. These attempts by families to fund for the treatments represent the hidden burden of rare diseases which has also been described in the Shire's Rare Disease Impact Report (2013) and Genetic Alliance UK report (2016). These methods are not only not sustainable but they are at high risk of accruing large amounts of debt due to the long-term need for treatments. From our consultations with the families, a number of parents have also resigned from their jobs as they need to care for their children and did not receive support from their employers. This undoubtedly adds further strain on their finances.

Medical bills directly due to the RD medical condition or even those directly un-related are not covered by insurance companies, which adds to the financial burden of the RD community.

Due to the poor job opportunities for disabled individuals in Malaysia, some have explored working from home or starting online businesses. However, it is often difficult to manage the business fulltime as the progress is sometimes limited by their own health or due to the fact that they are also at home caring for the affected child/children who need a lot of attention. Some funding to kickstart the businesses needed and to help them with some basic income at the early stages when they are not yet profitable. Some form of assistance is available from ministries and local governments (NST, 26 November 2018; Entrepeneurship Selangor;) as well as corporate bodies like the Yayasan MayBank RISE programme but individuals with RD and their carers need to compete with others with less severe conditions who may be more able to manage it as a fulltime careers and appear to be more 'marketable' to the potential sponsors. This is where the uniqueness of the RD community should perhaps be made part of the business model itself – and this approach is currently being pursued to some degree by the DON Management group, which is a talent and modelling agency that advocates for inclusiveness of differently-abled people in the fashion and media industry.

H. Psychosocial issues related to rare diseases

Unfortunately, there are no published reports of the psychosocial impact of RD in Malaysia, and this needs to be addressed urgently by the local healthcare professionals and public health experts in the country. Research into the psychosocial and economic aspects of RD should be supported and given appropriate funding. The studies such as these would be more informative if it is targeting concerns of a specific RD or to RDs that share similar medical conditions as this will help to identify the issues that are relevant to particular groups. However, most studies look across many different RDs to identify shared concerns. This would help to inform the ministries about the issues faced by those affected, and which solutions require advance planning, especially in areas of unmet needs and tackling mental health issues.

As there is no formal documentation of their voices, the Malaysian RD community has had to share its experiences through interviews with the mass media, and some insight can be gleaned from these reports into the challenges and issues faced by the community. There have been numerous studies that have been conducted across the world into this matter (as reviewed in von der Lippe et al., 2017). Both the informal interviews with the mass media and the formal published studies reflect largely the same issues – that living with RD impacts on wide-ranging aspects of life due to the medical constraints.

In 2013, the Rare Disease Impact Report surveyed communities in USA and UK totaling approximately 1000 individuals affected by 466 types of RD. This survey was commissioned by Shire, a biotech company researching into therapies for RD. Research by industrial partners in areas relevant to its own business interests should be treated with some caution but with transparency, no coercion and appropriate balanced reporting, research funds by industry can help to support work into understanding the issues faced by the RD community.

Findings from various reports often mention lack of awareness of the condition by healthcare professionals and the community as a significant psychosocial impact. The lack of knowledge by the healthcare professionals leads to anxiety and heightened psychological stress, as the patients deal with delays in diagnosis and treatment. Social isolation, financial worries and long-term psychological stress can lead to depression and anxiety amongst individuals with rare disease (as reviewed in Uhlenbusch et al., 2019). These mental health issues can also be experienced by the carers, who experience 'burn-out' and will inevitably reduce their quality of care (for some recent examples: Harrington et al., 2019 for lysosomal storage disorders; Cardinali et al., 2019; Canada Organisation of Rare Disorders Carer's report 2019).

Our consultation with the Malaysian RD community has also revealed that many patients and families experience the same issues as those in published reports. A particular point that was raised within the Malaysian RD community was the lack of access to certain drugs caused great anxiety and stress to the families – especially when they compare the situation to other countries and see the options that are available there, and wonder why those options are not offered in Malaysia. Therefore, undoubtedly this raises many psychological issues such as dissatisfaction, anger, feeling of hopelessness and frustration.

Another issue that was frequently raised as on the widespread discrimination that was faced by the RD community. In terms of education, RD children are often turned away due to fears of the school management that the school is not properly equipped to cater for special needs children, issues with disability access and the general perception that children with physical disabilities would 'do better' in special schools despite the fact that many of them would be able to cope with the normal curriculum. Recently, the Ministry of Education unrevealed the 'Zero-reject policy' of special needs children in education (NST,

30 October 2018), and the 2019 Budget allocated RM23 million towards funding for national schools to improve their infrastructure to become disabled friendly, both of which are steps in the right direction. However, the accompanying policy regarding institutions of higher learning to be disabled friendly within the next 10 years (The Star, 8 September 2019) is too distant a target and too many people within the RD community will fall through the cracks and be denied university education during this interim period.

Discrimination from the community towards people living with RDs often comes from lack of knowledge of the diseases. For example, patients affected by genetic skin disorders describe the unpleasant attention and hurtful comments from the public who wrongly perceive them to be infectious. Social media accounts offer an insight into the lives of people affected by RDs but it also opens them up to online bullying, as reported widely for a recent case of a person living with albinism. Other issues regarding lack of suitable public transportation or adequate understanding from providers of commercial transportation services also further adds to the feelings to depression and isolation faced by this community.

I. Support for carers

Caregiving is a long-term commitment and can be exhausting – financially, physically, emotionally and mentally. Patient support groups offer some comfort and support to families but it must be recognized that these groups are often managed by other carers who may be going through the same mental health issues and may not be able to offer appropriate advice. Thus, there must be a parallel support system for the families, or for the 'carers of the carers'.

Respite care currently comes from other family members or close friends who are familiar with the medical condition of the loved ones. However, since this is usually just available intermittently, the carers do not have a consistent opportunity for relief and to rejuvenate. In addition, carers who are also working often need to take time off from work to attend to their loved ones and this can cause friction with the employers. One recommendation is for a special 'compassionate leave' allocation (separate from their usual annual leave) to be provided to working carers if they need to take their loved ones to the hospital or other centres as part of their treatment.

Recognizing that this is an important aspect to address, recently the National Organization for Rare Disorders (NORD) launched a Rare Caregiver Respite Programme (www.rarediseases.org). This involves offering financial assistance to eligible caregivers (up to $500 annually) to pay for a allied health professional (for example, a registered nurse, licensed practise nurse, certified nursing assistant or home health aide) to provide respite care.

In addition, Eurordis has also recently introduced plans for a Eurordis integrated-care initiative in May 2019 (https://www.eurordis.org/carepaper). In the10-point position paper, recommendations were for countries across Europe to coordinate the network of government agencies that to provide holistic healthcare, social services, education, work-force participation of individuals and carers affected by RD. Another important recommendation was for European countries to put steps into place to guarantee that all people living with a rare disease and their carers are entitled to have access to a social worker. The social workers will then assist in providing respite care but also gather data for the ministries and agencies to determine the level of social protection and social inclusion provisions required. The social workers will then assist in providing respite care but also gather data for the ministries and agencies to determine the level of social protection and social inclusion provisions required. It is clear that Malaysia still lacks enough social workers for this initiative as recently the government revealed that the country has a very

low ratio of 1 social worker to 8,576 citizens, which is much lower than other countries like Singapore (1 in 3,448) (The Star, 2019). Recent announcement that social workers may soon be accorded professional status with the tabling of the Social Workers Professional Act in December 2019, will help to draw more into the profession (The Star, 2019) and give these critical healthcare providers the recognition that they deserve. Crucially, the Eurordis position paper calls for support groups to be recognized for their part as stakeholders in providing support to families, and calls for financial assistance to these organizations to fulfill this role more effectively. At present, organisations and support groups need to rely on donations and fundraising activities, which may not provide a consistent form of income. Thus, corporate companies are urged to consider providing long term financial support via their corporate social responsibility initiatives.

The number of people requiring palliative care in Malaysia was estimate to be a minimum of 32,000 individuals (The Star, 2015). However, this is likely to be a very conservative estimate. At the time of the report, there were 7 specialists with another ten under training (The Star, 2015). Thus, it can be projected that by 2025, there will be around 17 palliative care specialists to cater for a population of more than 30 million, giving a ratio of approximately 1 in 1.7 million. The ideal target should be 1 in 200,000. Therefore, career pathways for medical professionals to enter the palliative care speciality, with additional training on rare diseases, is urgently required.

The nursing profession in Malaysia could also contribute significantly to the palliative care environment in Malaysia and should follow the lead of the National Institute of Nursing Research (NINR), USA in their efforts to enhance the palliative care services within the country. In 2015, the NINR held an interdisciplinary workshop on the unique challenges in caregiving and palliative care in adult and pediatric rare diseases (Adams et al., 2016) and to identify gaps in the current care pathway. In the multi-ethnic and multi-religious community in Malaysia, there may be specific concerns pertinent to this population that is not relevant to those in the USA, therefore the palliative advisory committee in the Ministry of Health, the Malaysian Nursing Association together with other palliative care services such as Hospice Malaysia should take the lead to explore this further. This could involve having a workshop not just on the medical care but also together with the religious bodies to look into late stage care from the various perspectives of the religions and beliefs within the country.

J. Identifying prevention strategies for rare diseases

Prevention is better than cure. Nowhere is this adage more accurate than in the reduction of rare diseases. Prevention requires active program involving the whole population.

Preventive strategies may include the following interventions which were proven to be effective and reduce severe learning difficulties and physical handicap:

1. Pre-pregnancy and antenatal care

- Genetic counselling to at-risk individuals and families
- Preconceptional folic acid supplementation or folic acid food fortification
- Avoidance or reduction of exposure to teratogens

2. Maternal and neonatal screening programmes

- Maternal non-invasive prenatal screening and prenatal diagnosis
- Newborn screening for birth defects and inborn errors of metabolism (IEMs)

3. Public health strategies

- Role of general practitioners and public health planners
- Population carrier screening for rare diseases

While the majority of screening programs which are life-saving and lead to reduction of severe learning disabilities (from screening of rare inborn errors of metabolism or IEMs) are accepted by both medical and public, there are a number of issues pertaining to prevention of rare disease.

- Perception of discrimination i.e. reduction of rights and values of persons with rare disease ("search and destroy"). Individuals or survivors of rare diseases may perceive that termination of pregnancies because of severe rare diseases detected in-utero may diminish their societal standing and right to exist in the world.
- Population must be agreeable to be screened (Wilson and Junger, 1968)
- Programs such as prenatal diagnosis carry ethical, social and religious issues. For example is termination of pregnancies be accepted even though it is legal for maternal health reasons
- Infrastructure and funding for an already overburdened public health sector to carry out population-wide screening, counseling and referral to secondary and tertiary centres
- Educational and awareness program for public is needed before screening is done
- Continuing professional training for medical practitioners
- Support services e.g. laboratory and diagnostic services, imaging services, dietary services, genetic counselling services and provision of care and rehabilitation to those who were detected early.

Therefore proper planning and consultations with all stakeholders are required. Continuous monitoring, accurate registry data (pre and post screening) must be performed to allow cost-benefit studies to demonstrate cost-effectiveness and public acceptance. The classic criteria for population screening first advocated by Wilson and Jungner 1968 are still relevant for the majority of screening programs. See Box 1.

In addition, some population screening programs are not only life-saving, it may also be able to generate income that will cross-subsidise more expensive genetic or genomic testing. Therefore having a screening program will ensure that programs for rare diseases are sustainable in the long run.

Box 1: Wilson and Jungner classic screening criteria

1. The condition sought could be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceaptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to pissible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Recent relevant developments

A. Potential impacts of Health Technology Assessment and health economic models for access to orphan drugs

Publicly funded healthcare systems face difficult decisions about what level of access to provide to orphan drugs, given finite resources. Most publicly funded healthcare systems employ some form of cost-effectiveness analysis to decide whether or not a given treatment should be provided. This requirement is intended to ensure maximum benefit from the finite resources available. However, many orphan drugs can fall foul of cost-effectiveness criteria, given their high costs. Nonetheless, many public healthcare systems have decided to provide access for orphan drugs, with this decision based on a number of justifications beyond simple cost-effectiveness.

Some have argued on the basis of "equity", i.e. that public healthcare systems should target equal access to life saving treatment, in addition to seeking to maximise health gain across the whole population. Others have argued that rare diseases tend to have certain features that merit special consideration. These include the fact that children are often the patients, that the diseases are often highly debilitating; that the indirect costs (including on the family) are usually high among rare diseases; and that the rarity of the conditions results in high levels of unmet need, where little or no alternative treatment is available.

i. Amended Cost-Effectiveness Threshold for rare diseases

Some countries have adopted explicit cost effectiveness thresholds specifically for rare or ultra-rare diseases. A notable case is the cost effectiveness threshold used by the National Institute for Health and Clinical Excellence (NICE) in the UK. NICE has developed an assessment process for Highly Specialised Technologies (HST), defined as interventions for conditions with a prevalence of two per 100,000 or less. In 2016, NICE introduced a cost effectiveness threshold of GBP100,000 per Quality Adjusted Life Year (QALY) gained. The standard cost effectiveness threshold NICE applies in its standard Health Technology Assessment (HTA) process is GBP30,000 per QALY. Therefore, this represents an explicit dispensation with respect to the cost effectiveness for treatments for rare diseases.

ii. Weighted Cost-Effectiveness Threshold

Another mechanism to preserve the cost-effectiveness approach is to apply weights to cost-effectiveness thresholds to reflect the various considerations specific to rare diseases. Again, the HST program developed by NICE provides an example. Following a review in 2017, cost effectiveness in HST is judged more favourably if it is likely to extend life by more than 10 years. QALY gains between 11 and 29 years receive a weight between 1.1 and 2.9 and each QALY gained over 30 receives a weight of 3.

In theory, other weights could be included under a similar approach. For example, QALYs gained for children or younger adults could be weighted more highly than those gained for adults, to reflect a desire to prioritise health gains for younger people. Cost effectiveness calculations could also take greater account of the reduction of the indirect costs of disease reduced by treatment, for example if a given treatment reduced informal care requirements or other costs.

iii. Consideration of contextual factors

Healthcare systems can also account for contextual factors outside of the cost-effectiveness framework. Indeed, many countries do this. The NICE HST takes account of the impact of treatment of the family of the patient, but – as noted above – this is still within the context of a cost-effectiveness framework. The Ontario Public Drug Programs has developed a framework for evaluating orphan drugs, which does not target cost-effectiveness. The framework does include a threshold for rarity (one in 150,000 per year), and the value of drug is then determined on the basis of a range of factors.

In Korea, drugs can be designated as "essential" drugs, whereby they are exempted from cost-effectiveness evaluations. For a drug to be designated as "essential", it must meet the following criteria: (a) it has no alternatives (including alternative drugs and treatment methods); (b) it is used for treating serious life-threatening conditions; (c) it is used to treat small patient groups, such as those with rare diseases; and (d) it demonstrates significant improvement in clinical efficacy or survival.

iv. Formal analysis of contextual factors (MCDA)

Some researchers have proposed formalising the consideration of the contextual factors within a decision-making framework using multi-criteria decision analysis (MCDA). Under this approach, values and weights are assigned to each factor and combined through a formal process, with the rationale, scoring and methodology explicit. The perceived advantage of MCDA is that it is relatively transparent and rigorous, as opposed to a more subjective assessment of the various different factors. On the other hand, MCDA has been criticised for being arbitrary and channeling debate through the prism of a contrived scoring mechanism (Walker, 2016).

MCDA has not yet been used exclusively in HTAs in place of more traditional cost-effectiveness studies, although several public healthcare systems have on occasion adopted an MCDA-style approach, by formalising analysis of contextual factors alongside cost-effectiveness.

v. Accelerated approvals

Finally, most healthcare systems reflect certain considerations through accelerated approvals, to reduce the time for treatments to become available to patients. For example, France allows temporary authorisation for treatments of any rare disease considered to be imminently life-threatening and allows for fast-tracked review of drugs addressing unmet needs. Germany does not explicitly test for cost-effectiveness for individuals drugs and allows for more generous thresholds for statistical significance in its evaluation of clinical effectiveness for orphan drugs.

vi. The Malaysian Context

Malaysia employs an HTA process to evaluate new treatments and decide on the listing of new drugs. However, there is no specific approval mechanism for orphan drugs. Indeed, Shafie (2019) notes that generally orphan drugs are at a disadvantage as the Ministry of Health Medicines List Review Panel (MOHMLRP) rarely considers drugs that are designated for treating a small number of patients.

The current HTA process in Malaysia does not employ an explicit cost-effectiveness threshold, for orphan drugs or more generally. The HTA process does consider evidence in the form of Budget Impact

Assessments, but no explicit threshold is applied to new treatments. Various contextual factors are considered in the HTA process, but these are not formalised. There are ongoing investigations into the use of MCDA methods in Malaysia. For examples, Ramli et al. (2013) successfully employed an MCDA methodology to assess which statins should be maintained on the Ministry of Health Medicine Formulary

Recommendations for Malaysia

A. National policy on rare disease

1. A clear national policy on rare diseases and orphan drugs is needed

2. A Cabinet level paper on RD is recommended for further delibration and implementation in the medium term.

3. Preparation of draft legislation on Rare diseases and Orphan Drugs for submission for legal opinion and ethical and legal justifications for fair equity with allocation of resources for rare diseases.

4. Examine contraventions to Child Act 2001 and other international conventions in the protection of Child's rights, for example, failure to ensure and timely medical treatment for RD in babies and children, and non-compliance to the Disabilities Act in Malaysia and addressing these lacunae.

5. The United Nations General Assembly recommendations to be used as the source to provide Universal Health coverage for all.

6. Addressing and meeting Sustainable Development Goals (agenda 2030), in particular SDG number 3 on Health.

7. Fulfilment of the government's policy on Shared Prosperity Vision 2030, ensuring no one is left behind.

B. Orphan drugs and potential funding models

To help close the gap in accessing treatment the government needs to expand access to treatment and develop a sustainable financial model for rare diseases. The starting point for this financial model should be **reform of the current process to approve new drugs,** to take better account of the specific challenges of rare diseases. This reform could include explicit cost effectiveness and budget impact thresholds to control costs, but these should recognise the specific challenges of rare diseases. The government should consider how to reflect societal preferences to balance the priorities of equity and efficiency in the public healthcare system.

In the short to medium term, the only sustainable option for improving access to treatment is to increase government funding, and the government should develop a long-term plan to achieve this. However, there are also a number of measures the government could pursue to reduce costs and leverage other sources of funding as outlined below:

1. Private Insurance

In Malaysia, despite the existence of the public health system, a significant percentage of healthcare costs are borne privately. The average contribution of public healthcare expenditure was 52% in 1997 and it decline to 51% in 2014, meanwhile private healthcare expenditure contribution was 47% in 1997 and it increases to 48% in 2014 (Hameed et al., 2017). However, the bulk of private funding is OOP, rather than private insurance. OOP financing in Malaysia increased between 2003 and 2013, reaching 36% of total health expenditure. In contrast, only 8% of health expenditure came from private insurance, and only 1% from SOCSO/EPF, which can be characterised as social insurance. In part this can be explained by Malaysia's deliberate policy to promote a health tourism industry, whereby services are provided to private (usually international) patients.

The low level of health expenditure sourced from private insurance reflects the relatively low penetration of private insurance within Malaysia. The government has introduced personal income tax relief for life and health insurance to promote uptake. It is not clear how successful these schemes have been, but coverage remains low.

With respect to rare diseases, private insurance coverage in Malaysia is very limited as a result of the commercial disincentive to provide coverage to patients with genetic or pre-existing conditions, and the high costs of treatment for rare diseases.

There are two main policy levers to expand the role of private insurance with respect to rare diseases:

- In terms of regulation, the government could consider legislation similar to GINA in the US, to reduce discrimination on genetic grounds. This would broaden access to private insurance and reduce disincentives to undertake genetic testing. The government could go further and consider ACA-style regulation to remove consideration of pre-existing conditions and significantly strengthen the position of private insurance companies. However, such sweeping reforms would need to be considered in the broader context of the wider Malaysian healthcare system.

- The government could also expand incentives to the insurance industry. The principal mechanism to do this is through tax relief, which the government currently offers. However, the government could define a new level of insurance coverage as "advanced" (defined as providing cover for rare diseases) and introduce a higher level of tax relief for such policies. Alternatively, the government could share the costs of certain procedures and treatments, to improve the commercial viability. For example, the government could agree to split the cost of genetic testing with private insurers..

When considering how to proceed with respect to the private insurance industry, the government should consider that a regulatory approach is likely to result in increased costs for the consumer, particularly given the relatively small pool of policy holders. However, incentives are likely to be relatively slow in achieving broader coverage. Recognising this, and the fact that private insurance coverage is relatively low, the government should adopt a staged approach to developing private insurance coverage, balancing between regulation and incentives.

2. *Social Insurance*

Social insurance in Malaysia plays a relatively small role. EPF Account II withdrawals operate in a similar way to CPF Medisave in Singapore, except that Account II is not ring-fenced for healthcare can be used for a variety of other expenses, including in education. One option the government could consider is to create specific ring-fenced medical savings fund within EPF. However, in the context of addressing the challenge of financing treatments for rare diseases, this is unlikely to be helpful as savings are alone are unlikely to be sufficient.

The government could develop a scheme similar to Medshield Life in Singapore, operated by EPF. Under this scheme EPF members (employees and employers) would pay premiums alongside their monthly contributions to a social insurance fund, against which claims can be made for high healthcare costs. Significant work would need to be undertaken to establish how this system would interact with the current healthcare system. We know that in the case of rare diseases, there are gaps in access to treatment as a result of financing constraints. This is likely to be the case elsewhere across the public health system and there is unlikely to be broad political support for a nation-wide social insurance scheme catering for the costs of rare diseases. One option is to develop the scheme to address costs incurred in the public system above a point, regardless of condition. For example, the government could decide that the public system will meet the costs of treatment up to threshold, for example MYR500,000 at which point other sources must be found, including claims against the proposed social insurance scheme. This could help address the specific challenge of financing rare diseases, without being a rare disease-specific policy. Presumably, this would help address shortfalls in other areas. Further work would be required to establish the merits of such a scheme.

A more modest step would be to expand the scope of the mySalam scheme to support patients with rare diseases. Two steps would be needed, first to include rare disease on the list of critical illnesses to qualify for the scheme. Second, to including children in the scope of the scheme, such that parents receive benefits when their children are diagnosed.

3. *Trust Fund*

Some healthcare systems have established specific funds earmarked for use in certain areas, such as the Cancer Drug Fund in the UK which is used to provide interim funding while more comprehensive evidence is collected for new drugs. These funds can operate in different ways. Shafie (2019) notes that this type of funding has been criticized for being intrinsically unfair and unsustainable, for privileging certain illnesses over others for special treatment.

In the context of rare diseases specifically, there are two notable examples of ring fenced to consider. In Scotland the New Medicine Fund provides access to orphan drugs on a similar basis to the Cancer Drug Fund in the UK. Recently, Singapore established a new Rare Disease Fund specifically to support rare disease patients.

The Scottish fund is a ring-fenced allocation within the wider health budget. In contrast, the Singaporean fund leverages both government and private sources to operate on a trust fund model, which leverages contributions to generate interest which can be used to support patients.

The government could prioritize a trust fund arrangement, using existing structures. However, a number of issues would need to be addressed. The first challenge is sustainability. Although there is scope for charitable donations, this alone is unlikely to be insufficient to meet the costs of treatment and certainly not in the long term. The government can introduce various incentives to promote charitable donations, but this cannot be an alternative to government funding, if sustainable improvements in access to treatments are to be achieved. If the government decided to pursue an endowment model along the lines of the Singaporean model, then substantial upfront investment would be required. On the conservative assumption that the government could expect returns of 7.5% from a fund[1] then an initial fund size of between MYR500 million to MYR1 billion would provide a significant contribution. Matching the size of the Singapore fund, scaled to Malaysia population would require a fund of over MYR2 billion.

The second challenge is governance. It is important that access to any ring-fenced allocation is made on a fair and transparent basis. It must therefore be managed by the government, or by an independent body on the government's behalf. It is not advisable to pursue an arrangement whereby such a fund is managed directly by NGOs representing patients.

4. Price Negotiations

As recommended by Shafie (2019), the process of HTA should be more directly integrated with price negotiation in order to leverage on the clinical and economic assessment undertaken as part of the HTA. The government could also consider options to press its negotiating position, beyond the current PASc guidance. For example, the government could offer producers of specific treatments exclusivity for their treatments on the public health system beyond the patent term, in return for a reduction in the unit price of the treatment.

In the longer term, the government should develop a platform to procure drugs on a regional basis, to leverage broader purchasing power. An instructive example in the case of orphan drugs is the BeNeLuxa initiative 2018. Belgium, the Netherlands and Luxembourg established a cooperative initiative in 2015, subsequently joined by Austria in 2016 and Ireland in 2018. The initiative comprises extensive co-operation in informing and preparing pricing and reimbursement decisions, including joint HTA, horizon scanning, and the exchange of information from national disease registries, as well as joint price negotiations in industry- there is a clear case for Malaysia to advocate for such a platform. The lesson from BeNeLuxA, even in the case of relatively wealthy countries with similar levels of income, therefore demonstrate presumably similar healthcare spending appetites. The lesson from this case is that ASEAN is unlikely to be a suitable platform for such a mechanism, given the significant disparity in economic conditions. Rather, the government should pursue an ad-hoc arrangement, potentially within the looser APEC grouping.

[1] *Khazanah has a ten-year average of 11%*

C. Research and clinical trials of experimental drugs

Please refer to reference

Research on rare diseases and orphan drugs are limited in Malaysia. Many rare diseases hitherto unknown in the country are increasingly being reported. In addition, the natural history and long term outcome of many rare disease are poorly studied in the Malaysian population and dysmorphology in Asian children are difficult and lack normal data for comparison. There is lack of genomic data on the local population. The molecular basis for many rare or genetic diseases in Malaysia is unknown. Research funding are limited and many research projects on rare diseases are not approved due to the perception that there are little opportunities for 'commercialisation' or economic returns. Qualitative surveys, quality-of-life studies and psychosocial studies are urgently needed. Health economics and cost-effectiveness of treatment as well as cohort studies are seldom undertaken due to lack of sustainable long-term funding. Tissue bank and transplantation services are lacking due to insufficient resources.

Recent years saw collaborations with international centres. However, there is lack of opportunities to be the principal investigators in these collaborations. There is also interest in conducting clinical trials on rare diseases. Overall, the picture on research in rare diseases in Malaysia is rather dismal. However, there are a lot of potential opportunities for various studies as we have all the major ethnic groups in Asia. There is strong interest in rare diseases research as unlocking their pathophysiological processes have the potential to discover novel approach to treatment of common diseases and precision medicine.

D. Investments to develop talent and technology

1. Human resources planning and training: genetic counsellors, clinical geneticists, genetic nurses, genetic pathologists and technologists

A Master plan on the needs for services and manpower is required in keeping with international ratios, for example 2-4 clinical geneticists per million population and 2 genetic counsellors for each clinical geneticist. Similarly, retention of staff members must be enhanced by accelerating promotion and career incentives for staff members who are involved in the care and service of rare diseases.

2. Recognition and creation of posts in government and public companies

There must be official recognition by the government on new job descriptions e.g. genetic counselors, big data managers, molecular pathologists and creation of posts for these new jobs of the 21st century and reduction in clerical staff posts. Plans for re-skilling and re-training of government and private employees to these new careers are ideal.

3. Training, accreditation and privileging of qualified expertise

Government must play an active the role in selection of its staff meners for further training in the various fields mentioned above. In addition, it must work together with accreditation agencies such as MSQH to ensure standards and qualifications are maintained for these services.

4. Joint ventures, tax breaks and investments to develop local biotechnological companies to produce diagnostics and pharmaceuticals (biosimilars and novel drugs) for rare diseases

Many biologics and therapeutics and devices are at the end of their patent shelf life. We need to involve local pharmaceutical industry to capitalise on this as we have bioreactors and stringent food / pharma standards that can produce industrial-grade biosimilars, bioequivalents and intended copies. This may be in the form of incubators, joint ventures – even crowdfunding. Clinical trials on these products can be performed in Malaysia and regional countries

5. Increased funding for research in rare diseases pertaining to the local population

Draft industrial plans (e.g. MITI) to capitalize on health industries related to rare diseases e.g. actuarial data calculation for insurance; IR4.0 in terms of reporting and analytical systems for rare diseases; research in rare diseases to discover novel pathways and mechanisms for new biologics and devices.

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Research and Clinical trials in Malaysia

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IDEAS Research Paper: Rare Diseases - Fiscal Analysis

by Laurence Todd and Vaisnavi Mogan Rao

Executive Summary

Rare diseases are a significant burden to patients, their families and, more generally, society.

The government should develop a programme of **prevention and early detection** to reduce the prevalence of rare diseases and intervene early to provide the most effective treatment. There are a range of measures it can take to expand carrier and newborn screenings which are shown to be cost effective, and in some cases even cost saving.

When it comes to treatment, there is evidence of **significant gaps in terms of rare disease patients'** access to orphan drugs and other forms of care. To close this gap the government needs to expand access to treatment and develop a sustainable financial model for rare diseases.

The starting point for this financial model should be **reform of the current process to approve new drugs,** to take better account of the specific challenges of rare diseases. This reform could include explicit cost effectiveness and budget impact thresholds to control costs, but these should recognise the specific challenges of rare diseases. The government should consider how to reflect societal preferences to balance the priorities of equity and efficiency in the public healthcare system.

In the short to medium term the only sustainable option for improving access to treatment is to **increase government funding,** and the government should develop a long-term plan to achieve this. However, there are also a number of measures the government could pursue to reduce costs and leverage other sources of funding.

The government can leverage private sector and charitable support through tax incentives coupled with a **Trust Fund.** However, charitable sources alone will not offer a sustainable means to improving access to treatment. Furthermore, any trust fund arrangement must be governed on a fair and transparent basis.

The penetration of the **private insurance** market is relatively low in Malaysia, with the majority of private healthcare payments being made out of pocket. Furthermore, private insurers in Malaysia do not cover rare diseases. The government could begin to address this through a multi-stage approach, starting with the elimination of genetic discrimination. In the medium to longer term the government could pursue a broader strategy to increase the breadth and depth of private insurance coverage, but this would depend on wider decisions on the future of healthcare financing in Malaysia.

The role of **social insurance** is also limited in Malaysia. The government could develop a social insurance scheme, operated through EPF, to supplement the public healthcare system and manage high healthcare costs, such as those faced by rare disease patients. Further work would be required to establish how such a system would interact with the current public health system. Again, this is linked to wider decisions on the future of healthcare financing.

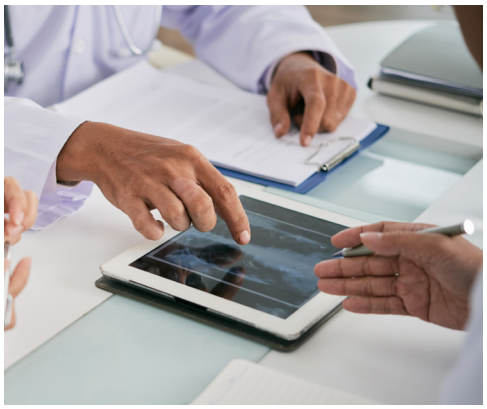
Finally, the government can pursue a number of options to **reduce the high price of treatment.** In the short term, the government should integrate price negotiations with health technology assessments; explore the potential of price/volume agreements and long term licensing; and develop tax incentives for Patient Access Schemes. In the longer term, the government should co-ordinate with international partners to establish a regional procurement platform.

Financial Model for Rare Diseases: Recommendations

Area	Short Term (within 1 Year)	Medium Term (within 3 -5 Years)	Long Term (5+ Years)
Public Financing	Develop a specific HTA process for orphan drugs, which takes account of a broad range of factors and accelerates and widens access to orphan drugs		
	Develop specific cost-effectiveness and budget impact thresholds		
	Establish societal preferences for prioritising access to limited resources		
	Increase the allocation for treating rare diseases, according to clinical need and a clear process		
Trust Fund	Establish clear governance structures for any trust fund arrangement		
	Leverage contributions from the private sector through tax incentives, alongside government funding, to support rare disease patients		
Private Insurance	Widen tax incentives to promote inclusion of rare diseases		Significantly expand the breadth and depth of private insurance through regulation and incentives, including for rare diseases
	Work with the insurance industry to remove genetic discrimination		
Social Insurance	Develop a social insurance scheme to supplement the public healthcare system and address high healthcare costs		
	Expand mySalam to cover rare diseases		
Price Negotiation	Explore the potential for price/volume agreements and long-term licensing to reduce prices		
	Introduce tax incentives for Patient Access Schemes		
	Establish a platform for regional procurement		

Key: Green = recommendation; Blue = choice/further work required

Introduction



National Policy on Rare Diseases Living with Dignity: In Search of Solutions for Rare Diseases (Thong & Azlina, 2018) set out the challenges for rare disease patients and their families in Malaysia. The paper identified a range of recommendations to address these challenges. *Improving Access to Orphan Drugs in Malaysia* (Shafie, 2019) expands specifically on the challenges to accessing orphan drugs. In this paper, we consider some of the recommendations presented in these publications in more detail, with a particular focus on exploring the government's options for developing a new financial model for rare diseases.

The paper is organised into four sections. The first section considers the **cost of rare diseases**. The second section considers the case for **increased prevention and early detection of rare diseases.** The third section considers the current level of **access to treatment.** The fourth section considers various **policy choices** in developing a financial model for rare diseases, building on proposals put forward in Shafie (2019).

Part 1: Cost of Rare Diseases

There is no single definition of rare diseases globally, but it is widely accepted that there are thousands of conditions. Although these conditions vary greatly, they often share certain traits, including lack of treatment, high rates of morbidity and mortality and high impact on children. In order to address the lack of treatment, various incentives have been introduced to promote the development of orphan drugs. The high research and development costs, coupled with high production costs and the relatively low revenues given the small patient population size, necessitate higher prices for these orphan drugs in order to ensure sufficient return on investment. As a result, the average prices of orphan drugs are higher than those for non-orphan drugs and can sometimes reach extremely high prices.

Given the high cost of these treatments, discussions on the cost of rare diseases often focus on orphan drugs. However, it is important to recognise that orphan drugs are only available for a minority of conditions and that only a minority of those drugs attract "blockbuster" prices. In this section we consider the various components that make up the total cost of rare diseases to patients, family and society, in order to provide context for the subsequent policy discussion.

Misdiagnosis and delayed diagnosis

Due to the number and variety of rare diseases, and relatively low levels of awareness among clinicians, prompt diagnosis of rare diseases can be challenging. This is true even in the most developed countries. A study by Black (2015) notes that "The medical journey travelled by patients with a rare disease (and their families) from initial disease recognition or onset of symptoms to a final diagnosis may involve serial referrals to several specialists and a plethora of, often invasive, tests. This odyssey can be prolonged and, as a result, have serious consequences for the health of patients." This "odyssey" can last several years: research by Shire (2013) finds that it took on average 7.6 and 5.6 years to secure a diagnosis in the US and UK respectively for rare diseases.

The diagnostic odyssey comes at a high price. Preliminary research by Imperial College Partners (2018) found that the cost of undiagnosed rare disease patients to the NHS was USD4.3 billion over the last 10 years. The average cost per undiagnosed rare disease patient over a ten-year period reached an average of USD16,497, compared to USD7,452 for the general hospital population during the same period that also had hospital visits.

Early and effective diagnosis can reduce these costs. A study in Lebanon (Khneisser, 2015) calculated the costs of expected care for inborn errors of metabolism, distinguishing between early and late diagnosis, found that early diagnosis (through Newborn Screening) resulted in a 50% reduction in direct healthcare costs.

Treatment, care and adaptations

Once diagnosed, treatment and care options can be considered. In some cases, treatment options will be available, including in the form of orphan drugs. In all other cases therapeutic and symptomatic care can be provided. This can include specialist equipment, for example, ventilators for patients who struggle to breath, including those suffering from Spinal Muscular Atrophy or specialist therapies, for example, physiotherapy for patients with impaired mobility. Beyond treatment and care, patients and their families often have to undertake lifestyle adaptations. This can include adaptations to the home to support the needs to mobility-impaired patients.

Delayed access to the appropriate treatment (including as a result of delayed diagnosis) can exacerbate the clinical manifestations of a condition, giving rise to complications that can incur additional costs. This can include a requirement to undergo surgery as a result of delayed access to the necessary treatment.

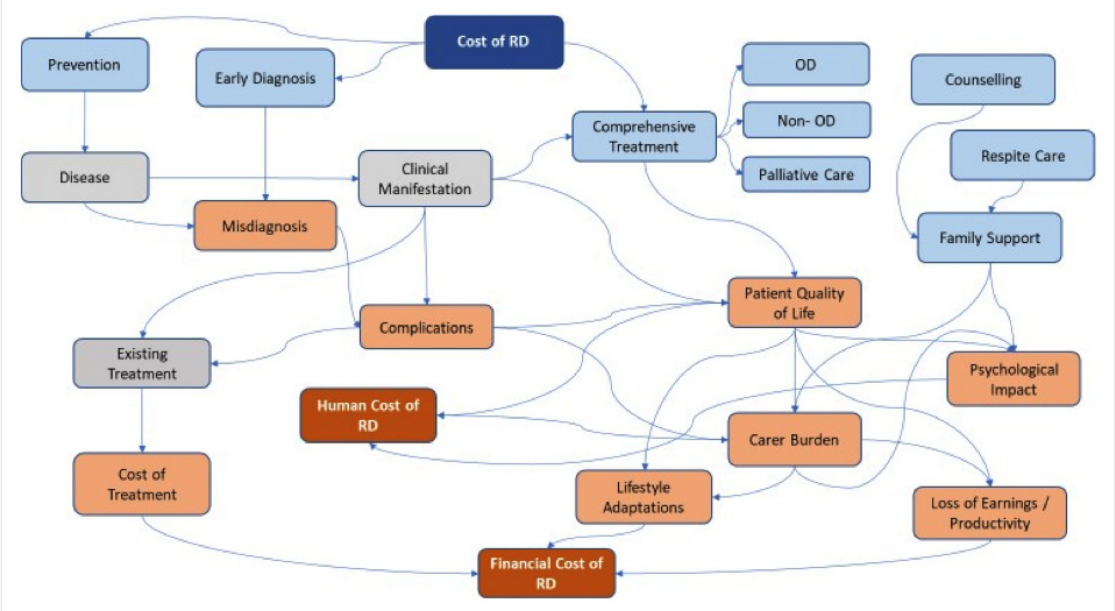
Quality of life, caregiver burden and loss of earnings/productivity

Given the high levels of morbidity associated with many rare diseases, the patients are often forced to bear a significantly reduced quality of life. Moreover, given the high requirement for care, parents and family members often have to step in as informal caregivers and also – given the complexity of the conditions – act as full time care coordinators. This results in significant loss of productivity and earnings for those patients of working age, and any family members that have been forced to give up work in order to provide care. Aside from the financial implications of rare diseases, a significant psycho-social burden is imposed on the patient and their family.

Quantifying the cost of rare diseases

Figure 1. below provides an overview of the various components of the cost of rare diseases.

Figure 1. Overview of Costs of Rare Diseases



Quantifying the financial costs of each component is challenging, given the heterogeneity of diseases and patient experiences and the fact that some aspects are inherently difficult to quantify, such as the psycho-social burden.

Cost-of-illness studies seek to quantify these various aspects where possible. Although such studies have not been widely undertaken in Malaysia for rare diseases, there are international studies which provide a point of reference. In particular, the BURQOL-RD project has developed a survey-based approach to identify the costs associated with a subset of rare diseases. The results for the rare diseases in this study most relevant in the Malaysia context are provided in the table below,

Table 1. Summary of Cost-of-illness findings for selected rare diseases (US dollar, various years between 2015-17)

Disease	Total Cost (Per Patient)	Healthcare Costs (Per Patient)	Non-Healthcare	Costs (Per Patient)
Fragile X	37,343	2,675	31,788	2,880
Mucopolysaccharidoses	85,663	55,967	27,930	1,766
Prader Wili Syndrome	49,201	12,793	35,115	1,293
Epidermolysis Bullosa	46,116	9,076	29,781	7,259

Source: BURQOL-RD

What we can see from these studies is that in most cases the higher costs are associated with non-healthcare costs, which include the costs of the provision of informal care by family members. The exception is MPS, which is not surprising given that expensive Enzyme Replacement Therapies (ERT) can be used to treat some MPS patients.

Conclusion

The cost of rare diseases are high, and the indirect costs are a major component. The costs of rare diseases are notably high across all categories. In most cases the indirect costs are the higher component, emphasising the burden that can fall on families and caregivers.

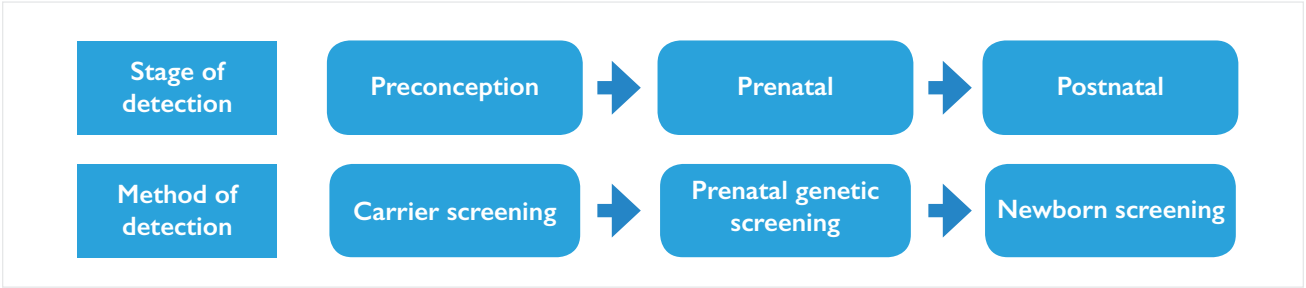
These costs are further exacerbated by delays in diagnosis and access to treatment. Diagnostic odysseys, which arise as a result of the complexity of rare diseases and lack of awareness among clinicians incur significant additional costs and can result in complications due to delays in access to treatment.

Part 2: Prevention and Early Detection

It is important to consider that most cases of genetic disorders end up in the public health hospitals for treatment. Therefore, a more cost-effective approach to rare disease is required through an enhanced prevention and early detection model. In this section we consider the government's options to improve prevention and early detection of rare diseases. In doing so, the government can reduce the prevalence of rare diseases and the costs associated with misdiagnosis and delayed diagnosis. We therefore consider these choices from a cost effectiveness perspective.

As illustrated in figure 2, prevention and early detection of these diseases can happen in several stages; preconception, prenatal and postnatal (early diagnosis).

Figure 2. Stages and methods of detection of genetic disorders



Carrier Screening and Expanded Carrier Screening (ECS)

Carrier screening identifies couples at high risk of conceiving offspring affected with serious heritable conditions. Identified couples are then exposed to facilitated reproductive decision making, including accepting risk, abstaining from conceiving, prenatal diagnosis (PNS), preimplantation genetic testing (PGD), using donor gametes or adoption. Expanded carrier screening (ECS) is offered to all individuals thus addressing the barriers of conventional carrier screening which is only carried out based on knowledge of familial history.

A study carried out in China (Zhao et al., 2018) illustrated the need to implement ECS. A total of 10,476 prenatal/preconception couples from 34 self-reported ethic groups were tested and analysed anonymously for 11 rare disorders. Findings revealed that 27.49% of individuals without self-reported family history of disorders were found to be carriers of at least 1 of the 11 conditions. Furthermore, 255 couples (2.43%) were identified as carrier couples at an elevated risk of having an affected baby, 65 of which would not have been identified through the existing strategy, which only detects thalassemia. The modelled risk of fetuses being affected by any of the selected disorders was 531 in 100,000 (95% CI, 497 – 567 per 100,000).

A US-based study (Beauchamp, 2019) investigated the cost effectiveness of ECS that assesses hundreds of conditions simultaneously over a minimal guideline of offering testing for cystic fibrosis and Spinal Muscular Atrophy (CF23 + SMA). The clinical benefits of screening (affected births averted, and life years gained) are largely attributable to diseases beyond CF23 + SMA. The cost effectiveness of ECS is estimated to be favourable, particularly when averted disease costs are considered and when compared against CF23 + SMA screening. Cost effectiveness analysis of this 176- condition screening programme showed that preconception ECS reduces the affected birth rate and is estimated to be cost effective.

Table 2 considers the findings from Beauchamp (2019). Table 2 presents the findings of the study in terms of Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) at different price points for the screening; different levels of effectiveness (50% of at risk parents intervening to avert a child born with disease, versus 77% of at risk parents intervening to avert a child born with disease).

Table 2. ICERs of ECS at different prices and intervention levels

	50%		77%		50%		77%	
Price (MYR)	3-Year Cost Saving (MYR)	Life-Time Cost Saving (MYR)	3-Year Cost Saving (MYR)	Life-Time Cost Saving (MYR)	3-Year ICER (MYR)	Lifetime-ICER (MYR)	3-Year ICER (MYR)	Lifetime -ICER (MYR)
2,070	840	6,728	1,288	10,304	122,958	-465,750	78,246	-823,446
2,898	840	6,728	1,288	10,304	205,758	-382,950	161,046	-740,646
4,140	840	6,728	1,288	10,304	329,958	-258,750	285,246	-616,446
10,350	840	6,728	1,288	10,304	950,958	362,250	906,246	4,554

Source: Beauchamp (2019), author's calculations

Table 2 shows that at a price of less that MYR 10,350 ($2,000) ECS will be cost saving, even at 50% effectiveness when considered over a lifetime. The market price is $690 (MYR 2,580).

Next Generation DNA Sequencing (NGS)

Azimi et al. (2016) evaluated the cost effectiveness of carrier screening using next generation DNA sequencing (NGS) by comparing the clinical and economic outcomes of NGS to either the absence of screening or traditional carrier screening for 14 diseases. They used a decision tree analysis to capture patient ethnicity, carrier prevalence for each disorder, detection rates, healthcare processes (eg. treatment for recessive disorders), patient behaviours and decisions (e.g., use of in vitro fertilization, pregnancy continuation) cost and health utilities. They modelled a population of 1,000,000 couples (representative of the US population) that contained 83,421 carriers of pathogenic mutation. NGS averted 21 additional births as compared to genotyping and reduced costs by approximately USD13 million. In comparison to no screening, NGS averted 223 additional affected births thus lowering total healthcare cost as compared with genotyping. Table 3 below shows the cost per - QALYs gained for conventional vs expanded carrier screening using NGS. In relation to clinical outcomes, it was argued that NGS provided higher detection rates for the most prevalent genetic disorders and can prevent and inform the majority of affected births.

Table 3. Cost effectiveness of expanded carrier screening using next generation sequencing.

	Conventional carrier screening	NGS Carrier Screening
Cost per life year gained	USD33, 812	USD29, 498
Cost for each affected birth avoided	USD1. 33 million	USD1.14 million

Source: : Azimi et al. (2016)

Newborn Screening

Newborn screening identifies early whether babies have acquired congenital birth defects or disorders. Newborn Screening (NBS) is practiced in Malaysia; see Loeng (2014) for a detailed discussion. At present, the only newborn screening programs offered to the full population in Malaysia are congenital hypothyroidism and G6PD deficiency. Thong and Azlina (2018) recommend NBS programmes targeting the following: i) inherited metabolic diseases; ii) critical congenital heart diseases; iii) primary immunodeficiencies; iv) spinal muscular atrophy type 1.

As with increased prevention, early detection through NBS can be cost saving, if the costs associated with late diagnosis are greater than those associated with timely treatment. Hatam et al. (2013) consider the cost effectiveness of NBS for phenylketonuria, congenital hypothyroidism, galactosemia, and favism. Their results are summarised in Table 4.

Table 4. Cost savings associated with NBS of PKU, CH, GAL and G6PD

Type of cost	PKU (USD)	CH (USD)	GAL (USD)	G6PD (USD)
Mean cost of screening	2.28	1.44	0.96	1.63
Cost of early treatment (screened patients)	7,037	1,014	4,243	3.2
Cost of delayed treatment (unscreened patients)	9,223	7,548	12,677	292

Source: Hatam et al. (2013)

Table 4 demonstrates how NBS can result in cost saving when the cost of treating patients early are lower than when diagnosis is delayed.

It is important to note that expansion of NBS will not necessarily be cost saving, given that early identification of a rare disease can increase the lifetime cost of treatment. However, expanded NBS can still be cost effective without be cost saving. Table 5 considers the ICER for expanded NBS of the conditions identified by Thong and Azlina and the conclusions reached in the respective studies.

Table 5. Cost Effectiveness of expanded NBS under various technologies

Condition	Country / Region of Study	ICER	Conclusion	Technology Used
IEM	Texas	USD 11,560	Cost Effective	MS/MS[1]
	California	USD 5,827	Cost Effective	MS/MS
Congenital Heart Disease	USA	USD 12,000	Cost Effective	Pulse Oximetry
	Washington State	USD 35,311	Cost Effective	TREC / DBS[3]
Primary Immunodeficiency[2]	Netherlands	EUR 33,400	Might be Cost Effective	TREC / DBS
	New Zealand	USD 30,409	Cost Effective	TREC / DBS
SMA	Washington State	N/A	No conclusion reached[4]	RT-PCR[5]

Source: Tiwana et al. (2012), Schoen et al. (2002), Grosse et al. (2017), Ding et al. (2016), Van der Ploeg et al. (2019), Health Partners Screening Group (2014), Chau et al. (2018)

[1] *Tandem Mass Spectrometry (MS/MS)*
[2] *All studies refer specifically to screening for Severe Combined Immunodeficiency Syndrome (SCID)*
[3] *T-cell receptor excision circle (TREC) assay with a dried blood spot (DBS)*
[4] *The study notes that early detection of SMA can result in significant clinical benefit if nusinersen is prescribed, but suggests further work is needed to establish cost effectiveness given the high cost of nusinersen*
[5] *Real-time polymerase chain reaction (RT-PCR)*

Table 5 demonstrates that in many cases expanded NBS for the conditions highlighted have been found to be cost effective.

Genomic Technologies

Introducing and integrating genomic technologies, such as whole exome sequencing (WES) into the healthcare system should also be explored. The clinical utility of WES has been shown to be beneficial to reducing the diagnostic odyssey in positive cases of genetic disorders. The use of WES is also cost effective as other time consuming and costly genetics tests prior to WES can be avoided. A study by Valencia et al (2015) found that 48% of patients has at least four genetic tests prior to WES and in some cases (> 10 genetic tests) the combination of these genetic tests cost more than WES itself.

Studies on the cost effectiveness of more widespread use of these technologies, however, are limited and further analyses needs to be done. In cases where timely diagnosis can have implications on the clinical manifestation of a disease or remove unnecessary healthcare costs, the use of genomic technologies should be considered. Therefore, at present the government should outsource these tests to overseas labs, where that is cost effective, whilst exploring the development of local labs.

Conclusions

The government should develop a programme of expanded carrier screening for rare diseases. Doing so will provide potential parents with greater choice and agency over how to proceed. From a financial perspective the result is likely to be a net cost saving, depending on the extent of intervention.

The government should also expand newborn screening, where it has been shown to be cost saving or cost effective. Based on international studies this is likely to include expanded NBS for inherited metabolic disorders, congenital heart disease and severe combined immunodeficiency syndrome. But evidence for expanding screening more broadly should also be sought. This should also include use of genomic technologies where possible and feasible.

Part 3: Access to Treatment in Malaysia

In this section, we consider the level of access to treatment for rare disease patients in Malaysia, focussing in particular on orphan drugs.

Access to orphan drugs in Malaysia

Shafie (2019) explains that there are two stages to treatment access. First, a drug must receive market authorisation after a review of its safety, efficacy and quality. Shafie suggests that availability can be defined as whether or not a drug has this market authorisation. In Malaysia, market authorisation, and thus availability of a drug, is decided by the National Pharmaceutical Regulatory Authority (NPRA). Once authorised, countries with public financing systems can decide to pay for a drug, and this decision is usually made on the basis of a Health Technology Assessment (HTA). Shafie suggests that accessibility should thus be defined as whether an individual is actually able to receive the drug in question. In Malaysia, HTAs for reimbursement (and hence decisions on drug accessibility) are conducted by the Pharmaceutical Services Programme (SPS) and – if successful – listed on the Ministry of Health Formulary (MOHF).

The number of orphan drugs on the MOHF is relatively low. Of over 180 orphan drugs authorised by the European Medicines Agency since 2001, we were only able to identify 20 which are listed on the MOHF. This compares to over 150 that have been listed in Germany. In 2015, over 100 orphan drugs were listed in Korea. In part this could be explained by differences in clinical requirements, but nonetheless this suggests that access to treatment for rare disease patients in Malaysia is generally lower than it could be, given the drugs which currently exist. Indeed, Shafie (2019) refers to a recent study in which he finds that only 60% of rare disease patients are receiving treatment.

However, among the drugs that have been listed are some of the most expensive orphan drugs available. Specifically, drugs classed as enzyme replacement therapies (ERT) for treating lysosomal storage disorders (LSD). These include drugs that can cost as much as MYR1 million per patient per year. But, listing on the formulary is not the end of the story, as Shafie (2019) notes. Not all patients eligible for ERT are able to receive the treatment, as the budget is very limited. We understand from clinicians that there are around five patients who could benefit from ERT but are currently on waiting lists. Of those that do receive ERT, roughly half of the cost is subsidised by MOH and the rest is sponsored by the pharmaceutical industry, charitable donations and private payments. The arrangements can vary from patient to patient.

Therefore, access to treatment is restricted in two senses, first in that fewer orphan drugs are listed on the formulary in the first place. And second, that budget limitations result in limited and uncertain access to those drugs which are listed. These issues raise concerns over access to newly available drugs which could have clinical utility in Malaysia – such as ataluren for Duchenne's Muscular Dystrophy (DMD) and nusinersen for Spinal Muscular Atrophy (SMA).

International comparison of expenditure on orphan drugs

An alternative method for assessing the relative level of access to orphan drugs in Malaysia is comparing Malaysia's expenditure internationally. There are two methodological challenges in undertaking this type of comparison. The first is that we do not have official statistics on Malaysia's expenditure on orphan drugs. We understand anecdotally that Hospital Kuala Lumpur (HKL) Genetics Department spends close to MYR30 million on treatments for rare diseases, including orphan drugs. On this basis we assume that Malaysia's total public expenditure on orphan drugs is MYR50 million, on the basis that there may be some expenditure elsewhere in the public health system. The second challenge is reflecting the relative income levels of different countries, and therefore establishing a "fair" comparison. We address this by comparing expenditure on orphan drugs as a percent of GDP per capita. Table 6 compares Malaysia's expenditure on orphan drugs to EU countries.

Table 6. International Comparison of Orphan Drug Expenditure

Country	OD expenditure ('000 euros) per 100,000 population (EUR)	GDP per capita (EUR)	OD expenditure per 100,000 / GDP per Capita
Austria	12,906	37,911	34.0%
Belgium	25,043	35,034	71.5%
Bulgaria	1,688	5,798	29.1%
Czech	4,836	15,005	32.2%
Hungary	4,100	10,274	39.9%
Poland	2,195	10,383	21.1%
Slovenia	9,633	17,426	55.3%
Malaysia	332	8,952	3.7%

Source: Szegedi et al (2018), author's calculations

Table 6 demonstrates that Malaysia spends significantly less on orphan drugs as a percent of GDP per capita than countries in Europe, including those which have similar (Hungary, Poland) or even lower (Bulgaria) levels of GDP per capita. There are a number of possible explanations for this. First is that we may be under representing the true extent of Malaysia's expenditure on orphan drugs. However, it would require that Malaysia as a whole be spending 5-10 times the amount that is being spent in HKL in order to close the gap. Second, is that the clinical needs in Malaysia are different from those in Europe. This is no doubt true but seems unlikely to account for the scale of difference. Third, is that that healthcare costs (including the price of orphan drugs) are higher in Europe and therefore expenditure is higher. Again, this is likely to be true to some extent but does not explain the scale of the gap. The most plausible explanation is that the level of access to orphan drugs in Malaysia is significantly lower than the level of access in Europe, even when accounting for relative levels of income.

Orphan drug expenditure versus total drug expenditure

Another important consideration in the context of international comparisons is whether the relative level of spending on orphan drugs is consistent with wider levels of healthcare spending. I.e. it is possible that Malaysia is spending less on orphan drugs, but that this is consistent with Malaysia generally spending less on healthcare. Table 7 below compares the expenditure by both Taiwan and Korea on all drugs and orphan drugs.

Table 7. Taiwan and Korea expenditure of all drugs and orphan drugs

	Taiwan (2014)	Korea (2015)
Population	22,610,000	51,470,000
Public Expenditure on Drugs (USD)	5,193,600,000	12,400,000,000
Per Capita	230	241
Public Expenditure on Orphan Drugs (USD)	121,000,000	195,000,000
Per Capita	5	4
OD as % of Drugs	2.3%	1.6%

Source: Hsu et al. (2018), Yoo et al. (2019)

Table 7 demonstrates that Korea spends relatively more than Taiwan per capita on drugs, but relatively less per capita on orphan drugs. It should be noted that since 2015 Korea has introduced a range of measures to improve access to orphan drugs.

Comparing these figures to the Malaysian case is difficult, given the lack of data and the fact that analysis of relative expenditures is highly sensitive to assumptions. In 2017, the MOH spent MYR2.382 billion on drugs (Pharmacy Services Programme, 2017). This is significantly less then is spent per capita in both Taiwan and Korea. If we consider orphan drugs, assuming that total drug expenditure is relatively unchanged and orphan drug expenditure is somewhere between MYR30 and MYR50 million, it is plausible to suggest that Malaysia's expenditure on orphan drugs is over 1% of total drug expenditure, close to Korea though still behind Taiwan. However, the figure is likely to drop below 1% if we count both public and private expenditure on drugs, given that most expenditure on orphan drugs is likely to occur in the public healthcare system.

Inpatient expenditure on rare diseases

Costs related to the treatment of rare diseases go beyond expenditure on orphan drugs. Another perspective to consider is inpatient expenditure. A study in Western Australia estimated the total inpatient expenditure on a cohort of rare disease patients. A study in Hong Kong adopted a similar method. The results are summarised in Table 8 below.

Table 8. Inpatient expenditure on rare disease patients in WA and HK

	Western Australia (2010)	Hong Kong (2015)
Prevalence of RD	2.0%	1.5%
Rare Disease Patients	61,279	109,535
Rare Disease Expenditure	AUD173,322,256	HKD1,594,339,530
Expenditure per RD patient (USD)	1,923	1,892

Source: Walker et al. (2017), Chiu et al. (2018)

Table 8 suggests similar levels of prevalence for rare diseases in Western Australia and Hong Kong, and both within the ranges identified within Europe. In both cases, expenditure on rare diseases patients is a greater proportion of total expenditure. Interestingly both studies yield similar estimates for expenditure per rare disease patient.

Comparing these figures to the Malaysian case is not possible. In this case, we do not have even anectodical information on inpatient expenditure for rare disease patients.

Therapeutic and symptomatic care

Treatment for rare diseases is not restricted to orphan drugs or inpatient treatment. Patients can also benefit from access to therapeutic and symptomatic care. Given the greater variety of possible interventions, it is difficult to systematically assess the level of access in Malaysia. During consultations with clinicians and patient groups multiple examples were given of cases where treatments were not provided by the public health system and had to be procured privately. Examples include the purchase of ventilators and physiotherapy.

Palliative care is also very important in end of life situations and families and caregivers can also benefit from respite care, which is often provided by charities. In Malaysia the provision of both palliative and respite care is relatively low.

Conclusions

The availability of orphan drugs in Malaysia is relatively low. The number of orphan drugs listed on the MOHF is lower than the number of orphan drugs listed in other countries. This is supported by anecdotal evidence from clinicians and patients.

Undertaking an international comparison on expenditure on rare diseases is challenging for a number of reasons. These include lack of comprehensive data on Malaysia, different approaches undertaken in different studies, lack of international agreed definitions among others.

Malaysia's spending on orphan drugs is low compared to other countries. Malaysia's per capita spending appears low when comparing to other countries, even when accounting for relative levels of income. It may be that this is consistent with a lower level of drug expenditure more generally, but it is difficult to draw concrete conclusions.

There are gaps in terms of access to other forms of treatment for rare diseases. There are anecdotal accounts of limited access to certain forms of symptomatic and therapeutic care, although it is difficult to provide a systematic assessment of the challenge given the lack of available data.

Part 4 Policy Choices: Improving Access to Treatment

In this section we assess various policy choices the government can consider to improve access to treatment, mostly building on recommendations presented in Shafie (2019). Specifically: i) reform of the process for providing orphan drugs on the public health system; ii) establishing a ring-fenced fund; iii) expanding the coverage of private insurance; iv) introducing social insurance and v) mechanisms to lower the price of treatment. In each case, we consider the policy choices in general terms before considering the Malaysian context.

Reforming the process for providing orphan drugs on the public health system

Publicly funded healthcare systems face difficult decisions about what level of access to provide to orphan drugs, given finite resources. Most publicly funded healthcare systems employ some form of cost-effectiveness analysis to decide whether or not a given treatment should be provided. This requirement is intended to ensure maximum benefit from the finite resources available. However, many orphan drugs can fall foul of cost-effectiveness criteria, given their high costs. Nonetheless, many public healthcare systems have decided to provide access for orphan drugs, with this decision based on a number of justifications beyond simple cost-effectiveness. Some have argued on the basis of "equity", i.e. that public healthcare systems should target equal access to life saving treatment, in addition to seeking to maximise health gain across the whole population. Some have also argued that rare diseases tend to have certain features that merit special consideration. These include the fact that children are often the patients, that the diseases are often highly debilitating; that the indirect costs (including on the family) are usually high among rare diseases; and that the rarity of the conditions results in high levels of unmet need, where little or no alternative treatment is available. Most public healthcare systems weigh these and other considerations to some degree but deciding precisely how much premium to accord these factors or exactly how to treat these considerations consistently across all decisions remains a vexed issue globally.

The extent to which these considerations have been formalised into explicit decision-making processes and how this has been done varies across public healthcare systems. Across these systems, various tools can be identified, which can overlap and be used in conjunction with one another.

Amended Cost-Effectiveness Threshold for rare diseases

Some countries have adopted explicit cost effectiveness thresholds specifically for rare or ultra-rare diseases. A notable case is the cost effectiveness threshold used by the National Institute for Health and Clinical Excellence (NICE) in the UK. NICE has developed an assessment process for Highly Specialised Technologies (HST), defined as interventions for conditions with a prevalence of two per 100,000 or less. In 2016, NICE introduced a cost effectiveness threshold of GBP100,000 per Quality Adjusted Life Year (QALY) gained. The standard cost effectiveness threshold NICE applies in its standard Health Technology Assessment (HTA) process is GBP30,000 per QALY. Therefore, this represents an explicit dispensation with respect to the cost effectiveness for treatments for rare diseases.

Weighted Cost-Effectiveness Threshold

Another mechanism to increase flexibility of the cost-effectiveness approach is to apply weights to cost-effectiveness thresholds to reflect the various considerations specific to rare diseases. Again, the HST program developed by NICE provides an example. Following a review in 2017, cost effectiveness in HST is judged more favourably if it likely to extend life by more than 10 years. QALY gains between 11and 29 years receive a weight between 1.1 and 2.9 and each QALY gained over 30 receives a weight of 3. An example of the application of this approach is provided below:

QALYs Gained	Treatment Cost (GBP)	Unweighted Cost Effectiveness (GBP / QALY)	Weighted Cost Effectiveness (GBP / QALY)
9	2,250,000	250,000	250,000
20	5,000,000	250,000	125,000
40	10,000,000	250,000	83,000

Source: NICE

In theory, other weights could be included under a similar approach. For example, QALYs gained for children or younger adults could be weighted more highly than those gained for adults, to reflect a desire to prioritise health gains for younger people. Cost effectiveness calculations could also take greater account of the reduction of the indirect costs of disease reduced by treatment, for example if a given treatment reduced informal care requirements or other costs.

Budget Impact Assessment

In addition to, or instead of, cost-effectiveness thresholds for assessing orphan drugs on an individual basis, many public healthcare systems assess the total budget impact of introducing a new orphan drug. This approach accounts for the cost, but also the total patient population. Despite the high costs for individual patients, the small population size means that the total cost of providing a new drug can be manageable. This, in combination with the challenges in assessing cost effectiveness, motivates countries to focus instead on the total cost. In some cases, this is done in conjunction with a cost- effectiveness assessment. For example, the NICE HST imposes a total budget impact threshold of GBP20 million per year of introducing a new drug. Other countries do not have an explicit cost- effectiveness threshold but do employ a total budget impact threshold for example neither France or Germany adopt an explicit cost-effectiveness threshold for orphan drugs but do set a total budget impact threshold of EUR30 million and EUR50 million per year respectively.

Consideration of contextual factors

Healthcare systems can also account for contextual factors outside of the cost-effectiveness framework. Indeed, many countries do this. The NICE HST takes account of the impact of treatment of the family of the patient, but – as noted above – this is till within the context of a cost-effectiveness framework. The Ontario Public Drug Programs has developed a framework for evaluating orphan drugs, which does not target cost-effectiveness. The framework does include a threshold for rarity (one in 150,000 per year), and the value of drug is then determined on the basis of a range of factors.

In Korea, drugs can be designated as "essential" drugs, whereby they are exempted from cost- effectiveness evaluations. For a drug to be designated as "essential", it must meet the following criteria: (a) it has no alternatives (including alternative drugs and treatment methods); (b) it is used for treating serious life-threatening conditions; (c) it is used to treat small patient groups, such as those with rare diseases; and (d) it demonstrates significant improvement in clinical efficacy or survival.

Formal analysis of contextual factors (MCDA)

Some researchers have proposed formalising the consideration of the contextual factors within a decision-making framework using multi-criteria decision analysis (MCDA). Under this approach, values and weights are assigned to each factor and combined through a formal process, with the rationale, scoring and methodology explicit. The perceived advantage of MCDA is that it is relatively transparent and rigorous, as opposed to a more subjective assessment of the various different factors. On the other hand, MCDA has been criticised for being arbitrary and channeling debate through the prism of a contrived scoring mechanism (Walker, 2016).

MCDA has not yet been used exclusively in HTAs in place of more traditional cost-effectiveness studies, although several public healthcare systems have on occasion adopted an MCDA-style approach, by formalising analysis of contextual factors alongside cost-effectiveness. The region of Lombardia in Italy has adopted an MCDA approach to regulate the introduction of new health technologies. Their MCDA is based on the framework proposed by The Evidence and Value: Impact on Decision Making (EVIDEM) group. The EVIDEM framework has also been used in Canada.

The Catalan Health Service in Spain (CatSalut) began an initiative on a multidimensional assessment of drugs value during the appraisal process. Guarga et al. (2019) conducted an assessment of a number of orphan drugs under the proposed framework. The study concluded that MCDA provided a useful framework, although it was noted by the decision making committee that it was more helpful to view the score for individual categories, rather than make decisions on a single aggregated score.

In 2012, Hughes-Wilson et al. developed an MCDA algorithm that assesses a medicine based on multiple criteria. This framework was tested against a set of orphan drugs by Schey et al. (2017). The framework is a relatively simple one that considers nine factors and accords each an ordinal score of up to three. Theses scores are then combined, and different weighting scenarios applied. The study found that a positive relationship between higher MCDA scores and the annual costs of drugs. The study noted numerous challenges with the model, including its relative simplicity and the suggestion that certain criteria (such as production complexity) reflected pharmaceutical considerations, rather than clinical priorities.

In an overview of the current practices of incorporating MCDA into HTAs, Marsh (2018) notes that Despite the attention given to debates in high income countries, an unusually large proportion of published studies on the use MCDA for HTA are undertaken in Lower and Middle Income Countries (LMICs, including Malaysia). Marsh suggests that this may be explained by the lack of established HTA methodologies in LMICs, allowing recent innovations to take hold.

Marsh (2018) concludes that these various studies crystallise a number of important lessons, with respect to the use of MCDA, including:

- The need to develop clear, transparent and non-overlapping criteria;

- The importance of providing a transparent assessment of different criteria, alongside any aggregate scores; and

- That MCDA provides a tool to prioritise between different choices within a clear context and fixed budgetary allocation.

The extent of the latter point is important within the context of this paper. Adopting a consistent approach to MCDA across all HTA decisions seems considerably more challenging that using MCDA to support decisions between individual treatments within a specific clinical context.

Accelerated approvals

Finally, most healthcare systems reflect certain considerations through accelerated approvals, to reduce the time it for treatments to become available to patients. For example, France allows temporary authorisation for treatments of any rare disease considered to be imminently life- threatening and allows for fast-tracked review of drugs addressing unmet needs. Germany does not explicitly test for cost-effectiveness for individuals drugs and allows for more generous thresholds for statistical significance in its evaluation of clinical effectiveness for orphan drugs.

Table 9. Summary of tools in deciding on provision of orphan drugs in public healthcare systems

Country	CET	CET Weights	BI Threshold	AA	MCDA
England	GBP100,000 / QALY	Gains exceeding 10 years weighted up to 30 years	GBP20m per year	Yes	Not explicit, contextual factors considered
Sweden	Not Explicit	No	Not explicit	Yes	Not explicit, contextual factors considered
France	Not explicit	No	EUR30m per year	Yes	Not explicit, contextual factors considered
Germany	Not explicit	No	EUR50m per year	Yes	Not explicit, contextual factors considered
Spain (Catalan)	Not explicit	No	Not Explicit	No	Yes
Malaysia	No	No	No	No	No

CET = *cost effectiveness threshold;* ***BI*** = *budget impact;* ***AA*** = *accelerated approvals;* ***MCDA*** = *multi criteria decision analysis*

The Malaysian Context

Malaysia employs an HTA process to evaluate new treatments and decide on the listing of new drugs. However, there is not specific approval mechanism for orphan drugs. Indeed, Shafie (2019) notes that generally orphan drugs are at a disadvantage as the Ministry of Health Medicines List Review Panel (MOHMLRP) rarely considers drugs that are designated for treating a small number of patients.

The current HTA process in Malaysia does not employ an explicit and flexible cost-effectiveness threshold, for orphan drugs or in general. The HTA process does consider evidence in the form of Budget Impact Assessments, but no explicit threshold is applied to new treatments. Various contextual factors are considered in the HTA process, but these are not formalised. There are ongoing investigations into the use of MCDA methods in Malaysia. For examples, Ramli et al. (2013) successfully employed an MCDA methodology to assess which statins should be maintained on the Ministry of Health Medicine Formulary.

Discussion

The Malaysian government could consider introducing an explicit cost-effectiveness threshold for new health technologies, similar to the NICE threshold, for orphan drugs and more generally across the healthcare system. The advantage of an explicit threshold is that it provides clarity and certainty over decisions whilst providing an element of cost control. However, it is challenging to articulate what such a threshold should be, particularly in the context of orphan drugs where any reasonable threshold is likely to be insufficient for some treatments. From a commercial negotiation perspective, an explicit threshold does provide a clear price signal to the pharmaceutical industry – in all treatments approved through the NICE HST, prices have been lowered in response to cost effectiveness concerns.

On the other hand, it could risk providing a "target" for industry to aim for. Any explicit cost- effectiveness threshold should be accompanied with an explicit total budget impact threshold.

As noted earlier, once certain orphan drugs have been approved in Malaysia, they are not necessarily provided to all eligible patients, due to budget constraints. This should be addressed, to provide greater certainty to patients and clinicians, such that all approved treatments are made available. The government can further strengthen its budget impact assessment to enable this, including considering application of a total budget impact threshold.

The Malaysian government could adapt an explicit cost-effectiveness threshold to reflect the particular challenges of orphan drugs through an increased threshold and / or a series of weightings to reflect certain concerns. In general, this has been the approach taken in the case of public healthcare systems which want to apply a specific cost-effectiveness threshold to orphan drugs (e.g. NICE). The advantage of this approach is that it maintains a cost-utility framework, preserving consistency across funding decisions. However, deciding on the weights is challenging and likely to attract criticism for arbitrarily over-valuing / under-valuing certain factors.

The current HTA process does take account of contextual factors, but this could be more formalised, including through more systematic adoption of an MCDA approach. Whether or not a single, consistent MCDA approach can be adopted across all healthcare assessments remains to be seen. In the shorter term, MCDA can provide a helpful tool to prioritise between different approaches with a specific clinical context.

These various choices should be combined in a new approvals process for orphan drugs, which also accounts for other factors beyond cost, including less clinical data.

Expanding the role of Private Insurance

Private healthcare payers typically fall into one of two categories: private insurance providers (either linked to individual or employer policies) or private individuals, in the form of out-of-pocket payments (OOP). In countries where private payers are the norm, such as the United States, then private insurance is widely used, as OOP at scale is unlikely to be sustainable given the lack of risk sharing.

In the USA, the high prices of orphan drugs have not been associated with lack of access through private insurance (ICER, 2017). This occurs because private insurance can adapt more flexibly to rising healthcare costs through adjusting premiums. Public healthcare systems, particularly those funded through general taxation are less flexible as taxes cannot so easily adjust to match continually changing healthcare demands. However, private insurance companies have expressed concerns regarding the rising costs of orphan drugs and are uncertain about how to manage these – Handfield and Feldstein (2013) found that 67% of US private insurance companies are concerned about orphan drugs, but only approximately 17% have developed meaningful strategies for addressing the cost of orphan drugs.

The US has taken a number of steps to improve access to treatments for patients suffering from rare diseases. In 2008 the Genetic Information Nondiscrimination Act (GINA) was passed into law, prohibiting discrimination by employers and health insurers. GINA prohibits health insurers from discrimination based on the genetic information of enrollees. Specifically, health insurers may not use genetic information to make eligibility, coverage, underwriting or premium-setting decisions. Furthermore, health insurers may not request or require individuals or their family members to undergo genetic testing or to provide genetic information. As defined in the law, genetic information includes family medical history, manifest disease in family members, and information regarding individuals' and family members' genetic tests.

These protections were further expanded under Affordable Care Act (ACA). A major provision of The ACA is to establish 'guaranteed issue'; issuers offering insurance in either the group or individual market must provide coverage for all individuals who request it. The law therefore prohibits issuers of health insurance from discriminating against patients with genetic diseases by refusing coverage because of 'pre-existing conditions'. As of January 1, 2014, applicants for comprehensive health insurance do not face questions about their health history. This is significant strengthening of private insurance customers, that benefits rare disease patients, although researchers have noted the challenges in implementing this provision in full (Sanford, 2014).

Tax Incentives

Alongside regulations such as these, countries have also pursued incentives to develop the coverage of private insurance, with mixed results. Australia introduced a tax penalty for individuals not conforming with the mandate to hold private health insurance. However, Stavrunova and Yerokhin (2014) find that despite the large tax penalty for not having private health insurance coverage relative to the cost of the cheapest eligible insurance policy, compliance with mandate is relatively low: the proportion of the population with coverage increases by only 6.5 percentage points (15.6%) at the income threshold where the tax penalty starts to apply.

In 1998 the Spanish government reformed its Personal Income tax allowance policy to abolish the tax relief for individually purchased policies and instead provide for tax allowances on policies taken out through employment. Rodriguez and Stoyanova (2007) find that total probability of buying personal health insurance was not significantly affected by the reform. Indeed, the fall in the demand for individual

policies (by 10% between 1997 and 2001) was offset by an increase in the demand for group employer-paid ones.

Both of these examples reflect more general attempts to incentivise broader coverage of private insurance. We could not identify any cases were incentives had been introduced to specifically promote coverage linked to rare diseases.

The Malaysian Context

In Malaysia, despite the existence of the public health system, a significant percentage of healthcare costs are borne privately. The average contribution of public healthcare expenditure was 52% in 1997 and it decline to 51% in 2014, meanwhile private healthcare expenditure contribution was 47% in 1997 and it increases to 48% in 2014 (Hameed et al., 2017). However, the bulk of private funding is OOP, rather than private insurance. OOP financing in Malaysia increased between 2003 and 2013, reaching 36% of total health expenditure. In contrast, only 8% of health expenditure came from private insurance, and only 1% from SOCSO/EPF, which can be characterised as social insurance. In part this can be explained by Malaysia's deliberate policy to promote a health tourism industry, whereby services are provided to private (usually international) patients.

The low level of health expenditure sourced from private insurance reflects the relatively low penetration of private insurance within Malaysia. The government has introduced personal income tax relief for life and health insurance to promote uptake. It is not clear how successful these schemes have been, but coverage remains low.

With respect to rare diseases, private insurance coverage in Malaysia is very limited. We could not identify any private insurance policies for individuals, which covered rare diseases, and this was confirmed by the insurance industry during stakeholder consultation. This was explained as a result of the commercial disincentive to provide coverage to patients with genetic or pre-existing conditions, and the high costs of treatment for rare diseases. There are cases of insurance policies held by employers which included coverage for genetically inherited rare diseases, but the examples identified were through international employers adopting a company wide policy, presumed to be based on prevailing practices in the US.

Discussion

The general criticism on the healthcare system predicated on private payers in the form of private health insurance are the lack of equity that can arise based on varying abilities to pay, and the high per capita healthcare costs. The advantage of relying on private insurance is that the market can respond more flexibly depending on commercial viability, reflected in faster access to more expensive treatments than in public-funded healthcare systems which typically operate from a principle of finite resources. In the US, the ACA sought to address the lack of equity whilst preserving the basic functioning of the private insurance market, by, on the one hand, strengthening customers' rights (e.g. no pre-existing conditions) whilst at the same time mandating wider uptake of insurance, thereby encouraging growth in the insurance firms' pool of customers.

Malaysia is in an interesting position of having both a public healthcare system, funded through general taxation and government revenue, as well as a large private healthcare system, albeit with relatively low levels of private insurance. The longer-term direction of Malaysian healthcare financing, either in favour of expansion of the public healthcare system and higher taxes, or through wider uptake of private insurance,

though a combination of incentives and regulation, goes beyond the issue of rare diseases. However, from a rare disease perspective, a public system can be broadly characterised as providing broader access on a more equal basis, but likely with a restricted access to the most expensive treatments, as public healthcare systems struggle to justify investment in relatively cost-ineffective treatments. In contrast, a private insurance system is likely to result in access to all treatments, but for a narrower segment of the population – specifically those with adequate insurance policies.

Setting aside this broader question, if the government chooses to develop the role of private insurance with respect to private insurance, there are a range of action they could consider. Broadly, these can be placed into two categories: i) regulations and ii) incentives.

- In terms of regulation, the government could consider legislation similar to GINA in the US, to reduce discrimination on genetic grounds. This would broaden access to private insurance and reduce disincentives to undertake genetic testing. The government could go further and consider ACA-style regulation to remove consideration of pre-existing conditions and significantly strengthen the position of private insurance companies. However, such sweeping reforms would need to be considered in the broader context of the wider Malaysian healthcare system.

- The government could also expand incentives to the insurance industry. The principal mechanism to do this is through tax relief, which the government currently offers. However, the government could define a new level of insurance coverage as "advanced" (defined as providing cover for rare diseases) and introduce a higher level of tax relief for such policies. Alternatively, the government could share the costs of certain procedures and treatments, to improve the commercial viability. For example, the government could agree to split the cost of genetic testing with private insurers.

When considering how to proceed with respect to the private insurance industry, the government should consider that a regulatory approach is likely to result in increased costs for the consumer, particularly given the relatively small pool of policyholders. However, incentives are likely to be relatively slow in achieving broader coverage. Recognising this, and the fact that private insurance coverage is relatively low, the government should adopt a staged approach to developing private insurance coverage, balancing between regulation and incentives.

Social Insurance

Many healthcare systems utilise social insurance schemes to finance healthcare costs, including several of those mentioned above. In many of these cases, social insurance is the sole method of public financing of healthcare.

Relevant to Malaysia are schemes whereby social insurance is a tool to supplement a broader public healthcare system. Singapore provides such an example. Singapore operates both a public and private healthcare system. Public hospitals are operated by government-linked companies and are available to citizens and prices subsidised by the government, whereas private hospitals are available at higher prices for private payers. The prices in public hospitals are means tested according to income. In addition, Singapore operates a number of savings and social insurance schemes. Members of the Central Provident Fund (CPF) contribute to a Medical Savings Account, which is used to meet medical expenses. The CPF also operates a social insurance scheme: MediShield Life, under which CPF members pay premiums in order to claim against high hospital bills and certain expensive outpatient treatments. MediShield Life operates on a non-profit basis, and therefore pays out around 100% of premiums received. Premiums

are also subsidised by the government. MediShield Life can be augmented through Integrated Plans (IPs), combining an element of private insurance offered by private insurers to provide additional benefits.

The Malaysia Context

Prior to 2019, in Malaysia there have been two notable cases of social health insurance. The first is withdrawals under the Employers Provident Fund (EPF). Workers and employers are required to make mandatory contributions (based on salary) to an EPF account. This contribution is split between Account I (70%) and Account II (30%). Withdrawals from Account II can be made in the course of an EPF member's working like to cover various costs, including education. The maximum that can a member ca withdraw is the full amount in their Account II. In that sense, health withdrawals under EPF are better categorised as a social saving scheme, as there is no pooling of risk on the basis of paid premiums. We understand that costs relating to rare diseases would I theory be eligible for EPF withdrawals, although in practice few members would have sufficient savings to cover the cost of expensive treatments, such as ERT.

The second scheme in Malaysia is the Social Security Organisation (PERKESO). Again, PERKESO operates on the basis of employer/employee contributions which in this case contribute to Employment Injury and Employment Invalidity schemes. These schemes offer various benefits, but these are linked to employment rather than to health per se. In some cases, these provisions could be relevant to rare disease patients. For example, if a PERKESO member developed a rare condition in adulthood that rendered them incapable of work, they could qualify for benefits under the Employment Invalidity scheme. However, these benefits are not intended to meet the costs of treatment and would likely be insufficient to do so. In any case, this cover would only apply in certain cases, and cannot be accessed more generally by rare disease patients.

In 2019, the government introduced a new form of social insurance called mySalam. MySalam is a free takaful income assistance scheme by the Pakatan Harapan Government which provides takaful protection for individuals in the B40 income group via the mySalam Trust Fund. Recipients of the Bantuan Sara Hidup (BSH) social security programme aged between 18 and 55 are eligible for mySalam coverage. Under the scheme, on diagnosis of one of 36 critical illnesses eligible recipients will receive a one-time MYR8,000 cash payout and M50 daily hospitalisation income replacement up to RM700 per annum at any government or qualified hospital. The intention of this benefit is to address loss of income associated with serious health conditions among the lower income group in Malaysia. The 36 critical illnesses specified by the scheme do not include rare diseases. Moreover, the benefits are restricted to working age recipients of BSH – in many cases with rare diseases patients are children. Finally, the MYR8,000 cash payout would be insufficient in many cases to cover the cost of treatment for rare diseases.

Discussion

The government could consider developing social insurance schemes to address the high costs of treating rare diseases. As with decisions over private insurance, this relates to wider questions over the future of healthcare financing in Malaysia, as the government needs to decide the balance between taxes, social insurance or private insurance in increasing healthcare financing.

As noted above, social insurance in Malaysia plays a relatively small role. EPF Account II withdrawals operate in a similar way to CPF Medisave in Singapore, except that Account II is not ring-fenced for healthcare can be used for a variety of other expenses, including in education. One option the government

could consider is to create specific ring-fenced medical savings fund within EPF. However, in the context of addressing the challenge of financing treatments for rare diseases, this is unlikely to be helpful as savings are alone are unlikely to be sufficient. Whether or not this would be a good step in the context of wider healthcare financing is moot for this paper.

The government could develop a scheme similar to Medshield Life in Singapore, operated by EPF. Under this scheme EPF members (employees and employers) would pay premiums alongside their monthly contributions to a social insurance fund, against which claims can be made for high healthcare costs. Significant work would need to be undertaken to establish how this system would interact with the current healthcare system. We know that in the case of rare diseases, there are gaps in access to treatment as a result of financing constraints. This is likely to be the case elsewhere across the public health system and there is unlikely to be broad political support for a nation-wide social insurance scheme catering for the costs of rare diseases. One option is to develop the scheme to address costs incurred in the public system above a point, regardless of condition. For example, the government could decide that the public system will meet the costs of treatment up to threshold, for example MYR500,000 at which point other sources must be found, including claims against the proposed social insurance scheme. This could help address the specific challenge of financing rare diseases, without being a rare disease-specific policy. Presumably, this would help address shortfalls in other areas. Further work would be required to establish the merits of such a scheme.

A more modest step would be to expand the scope of the mySalam scheme to support patients with rare diseases. Two steps would be needed, first to include rare disease on the list of critical illnesses to qualify for the scheme. Second, to including children in the scope of the scheme, such that parents receive benefits when their parents are diagnosed.

Price Negotiation

The high price of orphan drugs can be partially addressed through strengthening price negotiation. Across the public healthcare systems mentioned above, the HTA process is integrated into the price negotiation. Indeed, there is some evidence that a specific cost effectiveness threshold is helpful in achieving prices reductions – under the NICE HST most orphan drugs have been approved only following a reduction in price.

Many healthcare systems use Managed Entry Agreements to share the risk associated with a new drug between the government and the pharmaceutical industry. These can include agreements linked reimbursement to health outcomes. In Korea, the government and pharmaceutical companies share the uncertainties regarding the clinical outcomes of new drugs and their cost through a process of risk sharing agreements. A drug is eligible for a risk-sharing agreement if it satisfies the following criteria: (a) it should either be an anticancer agent or be used to treat serious, life-threatening conditions and should also lack alternatives or clinically equivalent drugs or treatments; and (b) the drug review committee concludes that further agreement on additional conditions is necessary after considering the severity of the disease, social influences, and other influences on public health. There are four types of risk-sharing agreements available: refunds, expenditure caps, utilization caps per patient, and refund/expenditure caps (Yoo, 2019).

The risk-sharing system in Korea was further expanded with the introduction of the cost-effectivness waiver system. Under this system, For cancer or orphan drugs that are clinically essential but cannot be

proven to have a significant improvement in clinical outcomes, only those that are listed in at least three of a group of seven reference nations can be included (after negotiation with the NHIS) without a cost-effectiveness evaluation. Since September 2016, all new drugs listed under the cost-effectiveness analysis waiver system are required to reach an expenditure cap risk-sharing agreement with the NHIS (Yoo, 2019). This is effectively a form of price / volume agreement.

Finally, it is important to note that many major developed markets have in place a number of incentives for the development of orphan drugs. In the main, these are intended to promote the discovery of new treatments, but they also include commercial incentives, such as longer exclusivity terms, which will have some bearing on price.

Biosimilars

An important consideration in the context of the prices of orphan drugs is the likely development path of the biosimilar market, the generic equivalent of complex biologics such as ERT.

The development of this market will have two important impacts, first in directly lowering the price of treatments as healthcare payers gain access to lower cost alternatives. And, second in strengthening the negotiating position of payers with the pharmaceutical industry as a result of increased competition. Judging the development of the biosimilar market is difficult. On the one hand, the patents on many orphan drugs have expired and yet there is no production of biosimilars. On the other hand, significant research and development is underway. Zhang (2016) argues that there will be significant growth in the availability of biosimilars for orphan drugs, and this will result in price reductions of 20% - 50 %.

In 2018, Japanese pharmaceutical producer, JCR Pharmaceuticals (JCR), announced that its agalisidase beta biosimilar had been approved and was being placed on the National Health Insurance (NHI) reimbursement price list and was being launched in Japan. The treatment will cost 25% less than the branded Fabrazyme and this occurred 12-15 years after that drug was first patented in Japan.

Table 10. JR-051, agalsidase biosimilar

Agalsidase Beta	USD Price
Fabrazyme (2007)	5,798
JR-051 (2019)	4,271
Price Reduction	26%

Source: biosimilardevelopment.com

Mulcahy et al. (2018) estimate that biosimilars will reduce direct spending on biologic drugs by USD54 billion from 2017 to 2026, or about 3% of total estimated biologic spending over the same period, with a range of USD24 to USD150 billion.

Regional Procurement

To address the high and rising cost of medical treatment some countries are pooling purchasing power. An instructive example in the case of orphan drugs is the he BeNeLuxa initiative 2018. Belgium, the Netherlands and Luxembourg established a cooperative initiative in 2015, subsequently joined by Austria in 2016 and Ireland in 2018. The initiative comprises extensive co-operation in informing and preparing pricing and reimbursement decisions, including joint HTA, horizon scanning, and the exchange of information from national disease registries, as well as joint price negotiations in industry (BeNeLuxA, 2018; Department of Health, 2018) – The focus is on high cost and orphan drugs considered priorities in each of the participating countries, and for which assessment methods are deemed sufficiently similar to allow for such co-operation.

The goals for different areas of collaboration in this initiative include

1) Joint horizon scanning

The aim is to highlight important pharmaceutical innovations before they reach the market and continually gather data and analyse research and literature. This will provide insight into expected costs, and enables timely decision making and (joint) price negotiations.

2) Joint Health Technology assessments

Building collaboration on supranational level, leading to joint health technology assessments to explore new mechanisms, ie: the mutual recognition of national assessments to reduce workload of national HTA - organisations.

3) Exchange of strategic information

Exchange information on medicine policies. Sharing of information and collaboration between countries, over an extended period of time, will benefit policy initiatives on pricing and reimbursement of medicines.

4) Joint price negotiations (though not joint procurement)

Working together will make it easier to negotiate medicine prices with the industry. Collaboration will allow countries to demand more transparency on the cost build up of pharmaceutical products. Increased transparency in pricing between countries is crucial to improvement medicine pricing.

In July 2018, the Dutch and Belgian Ministries of health announced their first joint market access deal for Biogen's Spinraza (nusinersen). The confidential pricing agreement gives Biogen temporary reimbursement of Spinraza until December 2020. Despite collaborations on HTA and price negotiations the two countries will differ in reimbursement of Spinraza; In the Netherlands the drugs are only reimbursed for patients up to the age of 9.5 years, subject to evidence of Spinraza's effectiveness in older patients, whilst Belgium will cover medicines for all age groups.

The Malaysian Context

Shafie (2019) notes that at present the HTA process in Malaysia is only used in the listing process and the pricing of drugs is undertaken separately by the Medicine Pricing Branch. Shafie (2019) suggests the price negotiation might not benefit from the extensive evaluation undertaken through the HTA as a result of this separation.

The Malaysian government has recently released guidance on Patient Access Schemes (PASc) which are a form of MEA. The guidance specifies qualifying schemes including those that involve clinical outcomes and financial components. We are not aware of any efforts by the Malaysian government to negotiation price / volume agreements.

The government does not offer any incentives for the development of orphan drugs. This is not surprising, given that the primary pharmaceutical development activities take place overseas. However, as a result Malaysia does not offer any commercial incentives which could be sued as leverage in price negotiations.

Malaysia does not currently participate in any regional procurement initiatives for orphan drugs.

Discussion

As recommended by Shafie (2019), the process of HTA should be more directly integrated with price negotiation in order to leverage on the clinical and economic assessment undertaken as part of the HTA. The government could also consider options to press its negotiating position, beyond the current PASc guidance. For example, the government could offer producers of specific treatments exclusivity for their treatments on the public health system beyond the patent term, in return for a reduction in the unit price of the treatment.

Table 11. considers a stylised scenario where for Drug A, initially priced at RM1,000,000 per year, a biosimilar is made available after 12 years at a reduced cost of 25%. Table 12 compares the total cost to government and total revenue to industry in a scenario where patent is provided for the usual 10 years, versus a scenario where a long-term license grants exclusivity for 30 years.

Table 11. Stylised Scenario for Long Term Licensing

Scenario: Standard Patent (10 years)	
Exclusivity Period	10
Unit Price Y1-15 (Original Patent Holder)	1,000,000
Unit Price Y15-30 (Biosimilar Producer)	750,000
Estimated 30-year revenue	15,000,000
Estimated 30-year cost	26,250,000
Scenario: Long Term License (30 years)	
Exclusivity Period	30
Unit Price Y1-30 (Original Patent Holder)	787,500
Estimated 30-year revenue	23,625,000
Estimated 30-year cost	23,625,000
Total Revenue Increase	58%
Total Cost Saving	-10%
Unit Cost Change Y1-15	-21%
Unit Cost Change Y15-30	+5%

Source: author's calculations

Of course, this is a stylised scenario, but it nonetheless presents the potential benefits to both government and industry of negotiating longer term exclusivity arraignments. Of course, the "loser" here is the generic/biosimilar producer and the government would want to take a view on the long- term benefit of incentivising development of this marker.

In the case of regional procurement, there is a clear case for Malaysia to advocate for such a platform. The lesson from BeNeLuxA, even in the case of relatively wealthy countries with similar levels of income, and therefore presumably similar healthcare spending appetites. The lesson from this case is that ASEAN is unlikely to be suitable platform for such a mechanism, given the significant disparity in economic conditions. Rather, the government should pursue an ad-hoc arrangement, potentially within the looser APEC grouping.

Ring Fenced Fund

Some healthcare systems have established specific funds earmarked for use in certain areas, such as the Cancer Drug Fund in the UK which is used to provide interim funding while more comprehensive evidence is collected for new drugs. These funds can operate in different ways. Shafie (2019) notes that this type of funding has been criticised for being intrinsically unfair and unsustainable, for privileging certain illnesses over others for special treatment.

In the context for rare diseases specifically, there are two notable examples of ring fenced to consider. In Scotland the New Medicine Fund provides access to orphan drugs on a similar basis to the Cancer Drug Fund in the UK. Recently, Singapore established a new Rare Disease Fund specifically to support rare disease patients. Table below compares the features of these two different funds.

Table 12. Comparison of Ring-Fenced Funds for Rare Diseases

	New Medicine Fund	Rare Disease Fund
Country	Scotland	Singapore
Fund Size	£80 million	S$70 million
Fund Type	Ring-fenced budget allocation, renewed every year	Endowment – interest generated is used to support patients.
Financing Source	Government	Government, and private donations. The government will triple match fund any charitable donations.
Scope	Supports health boards to fund the cost of orphan, ultra-orphan and end-of-life drugs for patients	To provide access to rare disease treatment for patients who cannot afford access
Approved treatments	All approved orphan drugs in Scotland	Five treatments approved at launch
Incentives	N/A	Donations are 250% tax deductible

The Scottish fund is a ring-fenced allocation within the wider health budget. In contrast, the Singaporean fund leverages both government and private sources to operate on a trust fund model, which leverages contributions to generate interest which can be used to support patients.

The Malaysian Context

Malaysia operates a range of Trust Funds within the healthcare system. These funds are used to leverage charitable donations to support patients. Donations have also been used in the past to support treatment cost for rare disease patients.

Discussion

The government could prioritise a trust fund arrangement, using existing structures. However, a number of issues would need to be addressed. The first challenge is sustainability. Although there is scope for charitable donations, this alone is unlikely to be insufficient to meet the costs of treatment and certainly not in the long term. The government can introduce various incentives to promote charitable donations, but this cannot be an alternative to government funding, if sustainable improvements in access to treatments are to be achieved. If the government decided to pursue an endowment model along the lines of the Singaporean model, then substantial upfront investment would be required. On the conservative assumption that the government could expect returns of 7.5% from a fund[6] then an initial fund size of between MYR500 million to MYR1 billion would provide a significant contribution. Matching the size of the Singapore fund, scaled to Malaysia population would require a fund of over MYR2 billion.

[6] *Khazanah has a ten-year average of 11%*

The second challenge is governance. It is important that access to any ring-fenced allocation is made on a fair and transparent basis. It must therefore be managed by the government, or by an independent body on the government's behalf. It is not advisable to pursue an arrangement whereby such a fund is managed directly by NGOs representing patients.

Summary of policy considerations

The government should **reform of the current process to approve new drugs,** to take better account of the specific challenges of rare diseases. This reform could include explicit cost effectiveness and budget impact thresholds to control costs, but these should recognise the specific challenges of rare diseases. The government should consider how to reflect societal preferences to balance the priorities of equity and efficiency in the public healthcare system.

In the short to medium term the only sustainable option for improving access to treatment is to **increase government funding,** and the government should develop a long-term plan to achieve this. However, there are also a number of measures the government could pursue to reduce costs and leverage other sources of funding.

The government can leverage private sector and charitable support through tax incentives coupled with a **Trust Fund.** However, charitable sources alone will not offer a sustainable means to improving access to treatment. Furthermore, any trust fund arrangement must be governed on a fair and transparent basis.

The penetration of the **private insurance** market is relatively low in Malaysia, with the majority of private healthcare payments being made out of pocket. Furthermore, private insurers in Malaysia do not cover rare diseases. The government could begin to address this through a multi-stage approach, starting with the elimination of genetic discrimination. In the medium to longer term the government could pursue a broader strategy to increase the breadth and depth of private insurance coverage, but this would depend on wider decisions on the future of healthcare financing in Malaysia.

The role of **social insurance** is also limited in Malaysia. The government could develop a social insurance scheme, operated through EPF, to supplement the public healthcare system and manage high healthcare costs, such as those faced by rare disease patients. Further work would be required to establish how such a system would interact with the current public health system. Again, this is linked to wider decisions on the future of healthcare financing.

Finally, the government can pursue a number of options to **reduce the high price of treatment.** In the short term, the government should integrate price negotiations with health technology assessments; explore the potential of price/volume agreements and long term licensing; and develop tax incentives for Patient Access Schemes. In the longer term, the government should co-ordinate with international partners to establish a regional procurement platform.

RD Fiscal Analysis Annex

This annexe presents simplified estimates of the fiscal impact of policies to prevent prevalence of Rare Diseases.

1. What is the fiscal impact of enhanced prevention through Expanded Carrier Screening (ECS)?

For this estimate, we consider Expanded Carrier Screen (ECS) as presented in Beauchamp (2019) which screens for 176 genetic conditions.

Parameters and assumptions

- We assume that the prevalence of At Risk Couples (ARCs) identified in the study sample would be the same in Malaysia;
- We assume that healthcare costs associated with treatment of the screened diseases are lower in Malaysia than the US. In order to quantify this, we use the estimates of international medical prices prepared by OECD (2017), which indexes healthcare costs with the OECD average as 100 (USA is 114). Malaysia is not included in this analysis, so we assume Malaysia's cost index would be 50 (i.e. healthcare costs are half those of the OECD);
- For our scenario, we assume that 250,000 birth couples are screened (to reflect roughly half of annual births in Malaysia);
- For our scenario, we assume that 50% of ARCs intervene to prevent an affected birth. The observed rate in Beauchamp (2019) is 77%; and
- We assume that the cost per screening is USD600, based on prices quoted by private providers. This price is not adjusted.

Calculations

Table A.1 below presents the findings from Beuchamp (2019) which are used for this estimate.

Table A.1 Results from Beauchamp (2019), all prices USD

Per Couple	Intervention Rate		
	100%	77%	50%
Averted Births	0.0029	0.00222	0.00145
Lifetime Costs Averted	3,249.88	2,489.27	1,624.94
3-Year Costs Averted	405.66	310.72	202.83
1-Year Costs Averted	130.10	99.65	65.05
Intervention Costs	159.77	122.38	79.89

Source: Beauchamp (2019)

Table A.2. below applies the findings from A.1 in a hypothetical population cohort of 250,000 birth couples, to reflect roughly half of annual births in Malaysia.

Table A.2 Findings from Beuchamp (2019) applied to population cohort of 250,000, all prices USD

Population Cohort (250,000)	Intervention Rate		
	100%	77%	50%
Averted Births	725	555	363
Lifetime Costs Averted	812,470,000	622,317,500	406,235,000
3-Year Costs Averted	101,415,000	77,680,000	50,707,500
1-Year Costs Averted	32,525,000	24,912,500	16,262,500
Intervention Costs	39,942,500	30,595,000	19,972,500

Source: Beauchamp (2019), author's calculations

Next we adjust the costs to reflect the fact that the cost of healthcare is generally lower in Malaysia than in the USA. For this we use estimates from OECD (2017) and assume that Malaysian healthcare costs would on average be 50% of those for the OECD (Table A.3).

Table A.3 International Health Price Index from OECD (2017), all prices in USD

Country	Index
USA	114
OECD	100
Malaysia (assumption)	50

Source: OECD (2017)

We apply the price adjustment from A.3 to the costs identified in A.2, below:

Table A.4 Estimated health costs averted, adjusted, all prices USD

Population Cohort	Intervention Rate		
	100%	77%	50%
Averted Births	725	555	363
Lifetime Costs Averted	356,346,491	272,946,272	178,173,246
3-Year Costs Averted	44,480,263	34,070,175	22,240,132
1-Year Costs Averted	14,265,351	10,926,535	7,132,675
Intervention Costs	17,518,640	13,418,860	8,759,868

Source: Beauchamp (2019), OECD (2017), author's calculations

Finally, we assume that screening price per couple is USD600, and we do not adjust this cost.

Table A.5 Estimated total screening costs and net savings, all prices USD

Population Cohort	Intervention Rate		
	100%	77%	50%
Screening Cost	150,000,000	150,000,000	150,000,000
Lifetime Costs Averted (Adjusted)	356,346,491	272,946,272	178,173,246
Net Cohort Saving	206,346,491	122,946,272	28,173,246

Source: author's calculations

On the basis of reasonably conservative assumptions, we estimate that ECS could save over USD28 million/MYR117 million in lifetime costs averted for a cohort of 250,000 birth couples.

Caveats

The savings represent a lifetime savings, against an up-front cost. The net costs in the early years would be negative for the cohort. The cost of screening subsequent cohorts could be less, as presumably each subsequent year's cohort of potential birth couples would include previously screened couples.

Table A.5 demonstrates that the overall cost-benefit of ECS will depend crucially on:
i) the price of screening per couple and; ii) the rate at which ARCs intervene to prevent an affected birth. At a higher price, or lower rate of intervention ECS might not be cost saving in Malaysia. But at a lower price, savings could be far greater. We cannot disaggregate this cost between costs borne by the public health system and privately by the patient. This estimate does not consider the ethical questions raised by introducing a policy intended to encourage couples to avert births.

2. What is the fiscal impact of food fortification with folic acid?

For this estimate, we considered the impact of food fortification with folic acid to prevent neural tube defects (NTDs).

Assumptions and parameters

The assumptions and parameters for this estimate are taken from various studies, detailed in Table A.6. The lifetime costs averted for NTD are adjusted according to the same method for the previous estimate, using table A.3.

Table A.6 Assumptions and parameters for folic acid estimate

Parameter	Value	Source
Population in Malaysia (2017)	31,520,000	World Bank
Annual births in Malaysia (2017)	508,685	DOSM (2018)
Prevalence of NTDs in Malaysia	0.42 per 1000 births	Boo et al. (2013)
Reduction in NTDs with 700mg folic acid fortification	30%	Grosse (2018)
Lifetime costs of NTDs	USD791,900	CDC (2017)
Lifetime costs of NTDs (adjusted)	USD347,325	CDC (2017), OECD (2017), author's calculations
Cost of food fortification per capita	USD0.065	Grosse (2018)

We apply the parameters in table A.3 to calculate the net saving for food fortification with folic acid in Malaysia, in a hypothetical scenario based on 2017.

Table A.7

Cohort	508,685
Averted NTD births	64
Averted Lifetime Costs	USD50,756,284
Averted Lifetime Costs (Adjusted)	USD22,261,528
Cost of food fortification	USD2,080,000
Net saving (2017)	USD20,181,528
Cost of food fortification per capita	$0.065

Source: as per Table A.6, author's calculations

On the basis of reasonably conservative assumptions, we estimate that food fortification with folic acid could reduce lifetime costs for each birth cohort by over USD20 million/MYR100 million.

Caveats

The savings represent lifetime savings, against an up-front cost. The net costs in the first few years would be negative for the cohort.

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