AN INSIGHT OF THE POLICY AND ACCESS TO ORPHAN DRUGS FOR TREATING RARE DISEASE IN MALAYSIA: QUANTITATIVE AND QUALITATIVE ANALYSIS

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UNIVERSITI SAINS MALAYSIA

2022

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by

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Thesis submitted in fulfilment of the requirements
for the degree of
Doctor of Philosophy

February 2022

ACKNOWLEDGEMENT

First and foremost, I am grateful to Allah the Almighty for blessing me with the strength and patience to complete this research. I would like to express my thanks and appreciation to my supervisor Assoc. Prof. Dr. Asrul Akmal Shafie, my co-supervisor Prof. Dr. Mohamed Azmi Ahmad Hassali and Prof. Dr. Nathorn Chaiyakunapruk for their guidance, advice, patience and suggestions throughout this research. It would be impossible to complete this research without their help, concern and consistent encouragement. I am greatly indebted and thankful to the Pharmacy Services Programme and Ministry of Health, Malaysia for offering me a scholarship and special thanks to the School of Pharmaceutical Sciences, Universiti Sains Malaysia, for providing me with the opportunity to further my postgraduate studies. Secondly, I would like to express my sincere appreciation to Dr. Keng Wee Teik (Geneticist and Head of Genetic Clinic, HKL), Dr. Ngu Lock Hock (Geneticist, HKL), Prof. Dr. Thong Meow Keong (Geneticist, UMMC), Dato' Hatijah Ayob (President of MRDS), Ir. Lee Yee Seng (President of MLDA), sisters and nurses who have helped me by providing brilliant ideas, advice, suggestions and facilities. Special thanks to my colleagues Haarathi, Siti Fauziah and other colleagues especially in the Pharmacy Practice and Development Division and also the Discipline of Social and Administrative Pharmacy who have directly or indirectly assisted me in this research. Last but not least, I would like to express my gratitude to my late grandmother Hjh. Yam Mat Dop, my parents Supian Ibrahim and Hjh. Maznon Jaafar who brought me up successfully and educated me to be what I am now; as well as my dear husband Zainudin Selamat and my daughter Nur Amanina Zahra. My thanks are also to

my in-law, brothers, sisters and my extended family for their encouragement and moral support.

May Allah bless the entire names above.

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LIST OF ABBREVIATIONS

AGSA	Association of Genetic Support of Australia
ASEAN	Association of Southeast Asia Nations
BMT	Bone Marrow Transplantation
CPAP	Continuous Positive Airway Pressure
DCA	Drug Control Authority
DRGD	Drug Registration Guidance Document
EMA	European Medicine Agency
ERT	Enzyme Replacement Therapy
EU	European Union
EURORDIS	European Organisation for Rare Diseases
FDA	Food and Drug Administration
GAGs	Glycosaminoglycans
GARD	Genetic and Rare Diseases Information Centers
GBP	British Pound Sterling
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HKL	Hospital Kuala Lumpur
HSCT	Hematopoietic Stem-Cell Transplantation
HUSM	Hospital Universiti Sains Malaysia
ICAP	International Compassionate Assistance Program
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
IEM	Inborn Errors of Metabolism
IMR	Institute for Medical Research
KFDA	Korean Food and Drug Administration
KORD	Korean Organisation for Rare Diseases
LSD	Lysosomal Storage Diseases
MAPS	Malaysian Association of Pharmaceutical Suppliers
MCDA	Multi-Criteria Decission Analysis

MLDA	Malaysia Lysosomal Diseases Association
MMS	Malaysia Metabolic Society
MNMP	The Malaysian National Medicines Policy
MOE	Ministry of Education
MOH	Ministry of Health, Malaysia
MOHMF	The Ministry of Health Medicine Formulary
MOPI	Malaysian Organisation of Pharmaceutical Industries
MPS (II)	Mucopolysaccharidosis (type II)
MRDS	Malaysian Rare Disorders Society
MYR	Malaysian ringgit
NGO	Non-governmental organisation
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NORD	National Organisation for Rare Disorders
NPRA	National Pharmaceutical Regulatory Agency, Malaysia
OOP	Out of Pocket
PASc	Patient Access Scheme
PhAMA	Pharmaceutical Association of Malaysia
PSOD	Philippine Society for Orphan Disorders
QoL	Quality of Life
RDSS	Rare Disorders Society Singapore
RVS	Rare Voices Australia
SEA	Southeast Asia
SMA	Spinal muscular atrophy
TFRD	Taiwan Foundation for Rare Disorders
TGA	Therapeutic Goods Administration
THB	Thai baht
UHC	Universal health coverage
UMMC	University Malaya Medical Centre
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
USA/USD	United States of America / United States Dollar
WHO	World Health Organisation

LIST OF APPENDICES

PEMAHAMAN TERHADAP POLISI DAN AKSES KEPADA UBAT *ORPHAN* BAGI MERAWAT PENYAKIT JARANG JUMPA DI MALAYSIA : ANALISA KUALITATIF DAN KUANTITATIF

ABSTRAK

Ubat *orphan* ialah ubat yang digunakan untuk merawat penyakit jarang jumpa. Penyakit ini mempunyai populasi yang sangat rendah dengan sebahagian besar penyakit ini akan melemahkan fungsi badan pesakit dan boleh mengancam nyawa. Kajian ini dijalankan dengan tujuan untuk menilai dasar penyakit jarang jumpa dan akses kepada ubat-ubatan *orphan* di Malaysia. Tiga fasa telah berjaya diselesaikan. Fasa pertama terdiri daripada kajian literatur untuk mengkaji status pengurusan penyakit jarang jumpa di Malaysia dan lima negara fokus lain (Filipina, Singapura, Indonesia, Vietnam, dan Thailand). Inisiatif pengurusan penyakit jarang jumpa di setiap negara dinilai berdasarkan kerangka tindakan *World Health Organisation* (WHO) untuk memperkasakan sistem kesihatan. Satu tinjauan keratan rentas dari sepuluh hospital awam juga dimasukkan dalam fasa ini untuk menganggarkan jumlah kes dan liputan rawatan untuk penyakit jarang jumpa di Malaysia. Fasa kedua pula dirancang dengan mengadakan 43 wawancara kualitatif dan satu perbincangan kumpulan fokus untuk mengetahui persepsi pemegang taruh kesihatan terhadap pengurusan penyakit jarang jumpa. Pada fasa terakhir, rekod perubatan bagi lima pesakit Mucopolysaccharidosis type II (MPS II) diambil, disemak dan dibandingkan dengan Garis Panduan Rawatan Penyakit Penyimpanan Lysosomal dengan Terapi Penggantian Enzim di Malaysia untuk menganggarkan kos yang terlibat dalam MPS II, termasuk rawatan dan pemantauan pesakit dari sudut perspektif penyedia

perkhidmatan kesihatan. Hasil kajian menunjukkan bahawa pengurusan penyakit jarang jumpa menghadapi cabaran yang besar di seluruh Asia Tenggara, merangkumi masalah sistem penjagaan kesihatan asas hingga kepada pembiayaan rawatan. Meskipun demikian, terdapat peluang yang besar untuk mengatasi masalah ini dengan mengadaptasi amalan terbaik penjagaan pesakit penyakit jarang jumpa ini dari seluruh dunia seterusnya mengatur pendekatan yang strategik oleh pelbagai pihak yang terlibat. Dari tinjauan yang dijalankan di fasiliti kesihatan awam, seramai 1,249 pesakit didiagnosis menghidap penyakit jarang jumpa. Namun, hanya 60% sahaja pesakit yang menerima rawatan ubat atau produk tambahan (suplemen), dan selebihnya meneruskan rawatan secara simtomatik. Secara amnya, pihak-pihak berkepentingan kesihatan berpuas hati dengan sistem kesihatan Malaysia dan pengurusan penyakit jarang jumpa masa kini berbanding dengan tahun-tahun sebelumnya. Walau bagaimanapun, masih terdapat banyak keperluan yang berpotensi untuk ditambah baik pada masa akan datang. Perbincangan kumpulan fokus juga membentangkan beberapa perkara dan perancangan bagi mencapai tujuan utamanya iaitu mengadakan akta penyakit jarang jumpa dan ubat *orphan* di Malaysia. Seterusnya, jumlah kos yang terlibat bagi seorang pesakit dalam pengurusan penyakit MPS II dan rawatan dengan ubat idursulfase pula adalah sebanyak RM710,289.35 setiap tahun. Kesimpulannya, Malaysia telah mencapai kemajuan luar biasa dalam menangani penyakit jarang jumpa, tetapi masih ada peluang untuk penambahbaikan. Untuk mengurangkan jurang akses kepada ubat *orphan*, semua pihak harus memahami dengan jelas pengurusan penyakit, struktur, dan rancangan nasional. Malaysia juga harus meneroka dan membentuk model kewangan baru bagi memastikan semua pesakit ini mendapat rawatan yang sepatutnya.

AN INSIGHT OF THE POLICY AND ACCESS TO ORPHAN DRUGS FOR TREATING RARE DISEASE IN MALAYSIA: QUANTITATIVE AND QUALITATIVE ANALYSIS

ABSTRACT

An orphan drug is a medicine used to treat rare diseases. The disease has a very low population, with most of the diseases will impair the patients' body functions and be life threatening. This study aimed to evaluate the rare disease policy and access to orphan drugs in Malaysia. Three phases have been completed. Phase one consisted of literature reviews to examine the current status of rare disease management in Malaysia and five other focus countries (Philippines, Singapore, Indonesia, Vietnam, and Thailand). They were examined based on the World Health Organisation's (WHO) framework for action in strengthening health systems. A cross-sectional survey from ten public hospitals was also included in this phase to estimate the number of cases and treatment coverage for rare diseases in Malaysia. The second phase was designed by conducting 43 qualitative interviews and a focus group discussion on describing the perceptions among health stakeholders towards rare disease management. In the final stage, five Mucopolysaccharidosis type II (MPS II) patients' record was retrieved and compared with the Guidelines for Treatment of Lysosomal Storage Diseases by Enzyme Replacement Therapy in Malaysia to estimate the costs involved in MPS II, including the treatment and monitoring patient from the point of healthcare provider perspective. The results suggest rare disease management remains challenging across Southeast Asia, as many of the focus countries face fundamental issues from basic healthcare systems to funding. Nonetheless, there are substantial improvement opportunities, including leveraging best practices

worldwide and organising a multi-stakeholder and regional approach and strategy. From the survey, 1,249 patients were diagnosed with rare diseases in public hospitals. However, only 60% received their medications or supplements, and the rest continued with symptomatic treatment. Generally, health stakeholders are quite satisfied with the Malaysia health system and rare disease management compared to previous years. However, there is still a need for more improvement in the future. The focus group discussion presented many points and planning, and their ultimate goal is to have Malaysian rare disease and orphan drug act. It is found that the total cost of treatment per patient per year with orphan drug idursulfase and management of MPS II is MYR 710,289.35. In conclusion, Malaysia has made tremendous progress in managing rare diseases, but there are still opportunities for development in critical areas. To reduce the gap access to orphan drugs, all parties must clearly understand the rare disease management, structure, and national plan. Malaysia also should explore and develop a new financial model to ensure rare disease patients receive the care they need.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Introduction

Many countries defined an orphan drug as medicine that is used to treat a rare disease. It is called "orphans" because most of the pharmaceutical industry has little interest in creating products intended to treat a small number of patients (Commission of The European Communities, 2008). More than 7,000 rare diseases exist, but only less than 10% have an effective treatment (Kaufmann, Pariser, & Austin, 2018). In Malaysia, for so many years, orphan drugs were mainly concentrated on products which not commercially viable to supply only. Until 2012, the policymakers redefined the orphan drug definition in the second edition of the Malaysian National Medicine Policy (MNMP). It becomes a medicine, vaccine or in vivo diagnostic agent intended to treat, prevent or diagnose a rare disease or not commercially viable to supply to treat, prevent or diagnose another disease or condition (Ministry of Health Malaysia, 2012).

Meanwhile, the term rare disease (orphan disease) is used to designate illnesses that affect only small individuals or a small percentage of the population. It is a severe disease and life-threatening or chronically debilitating (The European Parliament and of The Council, 2000). Most rare diseases are genetic origins (80%) and appear early in life (Kaplan et al., 2013). According to the European Society of Paediatric Oncology, 75% of rare diseases affect children, of whom 30% die before reaching their fifth birthday (The European Society of Paediatric Oncology, 2014). Research has shown that some rare diseases have a more harmful effect on health-related quality of life (QoL) than other serious diseases. However, it is always subject to the nature of individuals' perceptions

and factors beyond the influence of the physical manifestation of their QoL (Cohen & Biesecker, 2010). Information about rare diseases is often inadequate as it seldom occurs in the country and has low awareness and training among healthcare providers. As a result, they hardly diagnose the condition correctly and cause optimum or adequate treatment, unable to be achieved (Sharma, Jacob, Tandon, & Kumar, 2010).

Many references estimated 6,000 to 8,000 types of rare diseases existing globally that can be grouped according to their manifestations (Department of Health UK, 2013b; Genetic and Rare Diseases Information Center, 2017; Gupta, 2012; Rare Diseases Europe, 2009). Lysosomal storage diseases (LSDs) are examples of rare disease groups, which contain more than 40 rare inherited metabolic disorders, including Mucopolysaccharidosis (MPS) (Winchester, Vellodi, & Young, 2000). These diseases are caused by the absence or deficiency of lysosomal organelles containing primary digestive enzymes that break down the complex cellular components such as protein into simple parts. LSDs are heterogeneous and inherited metabolic disorders. Due to the lack of enzymes, the macromolecules are not digested properly and accumulate in the cells (Platt, d'Azzo, Davidson, Neufeld, & Tifft, 2018; Schuchman & Wasserstein, 2018). As a result, patients will experience cellular dysfunction and clinical abnormalities related to the nervous system and connective tissue such as the skeleton, brain, skin, heart, and central nervous system.

The MPS is the largest group in the LSD family. The MPS type II, known as Hunter disease, is the most common disease (Sun, 2018) among the MPS group. It involves the lysosomal enzymes' defective activity, which leads to abnormal accumulation of glycosaminoglycans (GAGs), heparin sulfate, dermatan sulfate, and chondroitin sulfate

(Mashima, Sakai, Tanaka, Kosuga, & Okuyama, 2016). The manifestation of individuals with MPS II is healthy initially in childhood. However, later issues appear which involve multiple organ systems such as cardiovascular disease, pulmonary disease, and central nervous system disease. There is no cure for MPS II. Treatment involves managing symptoms and complications. Patients need an enzyme called iduronate-2-sulfatase (idursulfase), registered as an orphan drug in 2001, to break down the accumulation of substances in the body (European Medicines Agency, 2016).

The availability and accessibility of orphan drugs are essential to reduce morbidity, mortality and increase the quality of life among rare disease patients. Despite the need and importance of early treatment, there is a lack of access to orphan drugs (Gammie, Lu, & Babar, 2015). Melnikova (2012) reported that less than one in ten patients with rare diseases receive disease-specific treatment (Melnikova, 2012). It is always debated as the high cost of treating a single rare disease patient results in unfavourable cost-effective studies (Pearson, Rothwell, Olaye, & Knight, 2018). For instance, the orphan drug Alglucosidase alfa injection to treat Pompe disease in Malaysia may cost about MYR 1.2 million per patient each year compared to Amlodipine 5mg tablet antihypertensive to treat hypertension costs only MYR 9.53 (MYR 2.61/100's) per patient. Nevertheless, the annual budgetary impact on treating ten eligible Pompe disease patients will be only MYR 12 million compared to Amlodipine which was MYR 55 million due to the high prevalence (30.3%) of hypertension (Institute for Public Health, 2015; Pharmaceutical Services Programme, 2020).

Generally, access to orphan drugs is a growing issue for Malaysian healthcare decision-makers. Increasingly are the concerns amongst governments or decision-makers

related to patient access, affordability and estimation on the future budget impact of orphan drugs. To date, orphan drugs for rare disease patients have only accounted for a small percentage of the overall budget.

1.2 Aims of the study

General objective:

To evaluate the rare disease policy and access to orphan drugs in Malaysia.

Specific objectives:

i. To describe the state of rare disease and access to orphan drugs in Malaysia.
ii. To compare rare disease management with other countries in Southeast Asia.
iii. To describe the patients' perception of rare disease management in Malaysia
iv. To estimate the cost of treating MPS II

1.3 Justification of the study

The MNMP, which the Malaysian Cabinet endorsed in October 2006, is the way forward for the nation to ensure optimum medicines management for all Malaysians' better health outcomes. Since the first edition, the objectives of the MNMP is to promote equitable access and rational use of safe, effective, and affordable essential medicines of good quality to improve the health outcomes of the people. One of the core components in MNMP is Access to Medicines towards achieving optimal health outcomes. Unfortunately, most rare disease patients receive little attention from the government and

also the public. There is no specific act, system, a guideline for rare diseases and orphan drugs yet in Malaysia to cater to this issue. It seems that they had overlooked or a very minimal discussion from the policy-makers, higher authorities, ministries, or even politicians.

In reality, caregivers primarily suffer from finding appropriate tests, medical treatment, dealing with financial factors. These will exacerbate the emotional challenges experienced by rare disease patients and families. On the other hand, physicians reported that adequate and effective treatments are less available, which adds to doctors' time finding solutions for their patients. The emotional impact on patients suffering from treatable and untreatable rare diseases is significant (Nunn, 2017). They require financial support and other additional support services, such as patient education, mental health services, and referrals to support organisations. Although it only affects a minimal number of patients, it will have a significant impact in the long run.

The data collected and results through this study may provide policymakers and healthcare providers with information to improve rare disease management by taking examples and actions that other reference countries have taken to address these rare diseases (adopt and adapt). Meanwhile, the calculation of the costs involved in inpatient care may give ideas to the policymakers on the plan of action that should be taken to enable these rare disease patients to get the treatment they deserve.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This literature review chapter aims to explore the state of rare disease and orphan drugs in the world and Malaysian setting. It may identify the literature gaps that require further investigations to answer the problems related to better healthcare among all stakeholders involved. This chapter has five related subtopics. First, the overview of rare diseases from the definition until issues related to it. Second, the overview treatment option for rare diseases, specifically orphan drug descriptions until issues related to orphan drugs. Third, the policy and management of rare diseases in the world. This section describes the policies, regulations, and programmes in referral countries. Fourth, all about MPS, one of the rare disease groups. This section describes the MPS group and the details of MPS II. Lastly, an overview of the healthcare system in Malaysia in general. This final section in the literature review explains the status of healthcare services and policies towards access to medicine in Malaysia.

2.2 Rare disease

2.2.1 Definition of rare disease

The definition of a rare disease is different according to each country and prevalence. The definite number of rare diseases is difficult to determine, as it always depends on the definition (Aymé, Bellet, & Rath, 2015). Table 2.1 and Figure 2.1 shows the definition and prevalence of the rare disease in a few reference countries (Lang &

Wood, 1999; Song, Gao, Inagaki, Kokudo, & Tang, 2012a, 2012b; The European Parliament and of The Council of the European Union, 2000). In Europe, a disease is considered a rare disease when it affects less than 1 in 2,000 citizens (Orphan Drug Regulation 141/2000) and may affect 30 million European Union citizens (The European Parliament and of The Council, 2000). All six reference countries have their definition of a rare disease (Table 2.1). Although Malaysia has no official definition for rare diseases yet, the Malaysian Rare Disorder Society defines a rare condition when the prevalence is less than 1 per 4,000 in the community (Malaysia Rare Disorders Society, 2013).

Table 2.1 Definition of rare disease in six reference countries

Country	**Definition of rare disease**
European Union	A disease is defined as rare in the European Union when it affects fewer than 5 in 10,000 citizens
United State	A disease is defined as rare when it affects fewer than 200,000 people in the United States
Australia	A disease that occurs in less than 1 in 2000 people in Australia
Japan	A disease of unknown aetiology with no effective treatment that presents a major financial and psychological burden and that is rare (less than 50,000 total patients)
South Korea	A disease that affects fewer than 20,000 people and appropriate treatment has yet to develop.
Taiwan	A disease occur fewer than 1 in 10,000 population which has a genetic origin and difficult to diagnose and treat

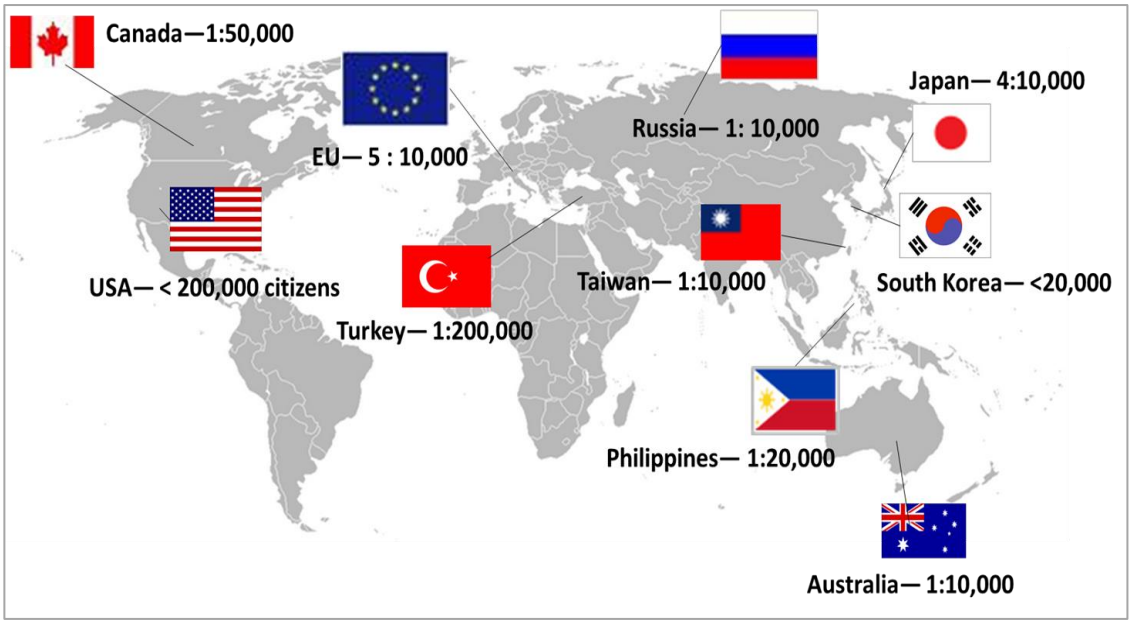

Figure 2.1 Prevalence of rare disease in ten main countries

Meanwhile, Figure 2.2 shows the study by Schey et al. on rare disease growth in Europe. The rate of rare diseases increased more rapidly in 2002 - 2010, which is approximately a 10% increment per year (Schey, Milanova, & Hutchings, 2011). The trend is towards a steady escalation in the cumulative number of rare diseases, averaging just over five new diseases per year over the 20 years of the model. Because of the increasing number of rare diseases, governments and decision-makers are concerned about orphan drugs. A study has estimated that between eight and twelve orphan new medicines will be approved in Europe per year (2009-2019), compared to the average of six between 2001 and 2010 (Rare Diseases Europe, 2009).

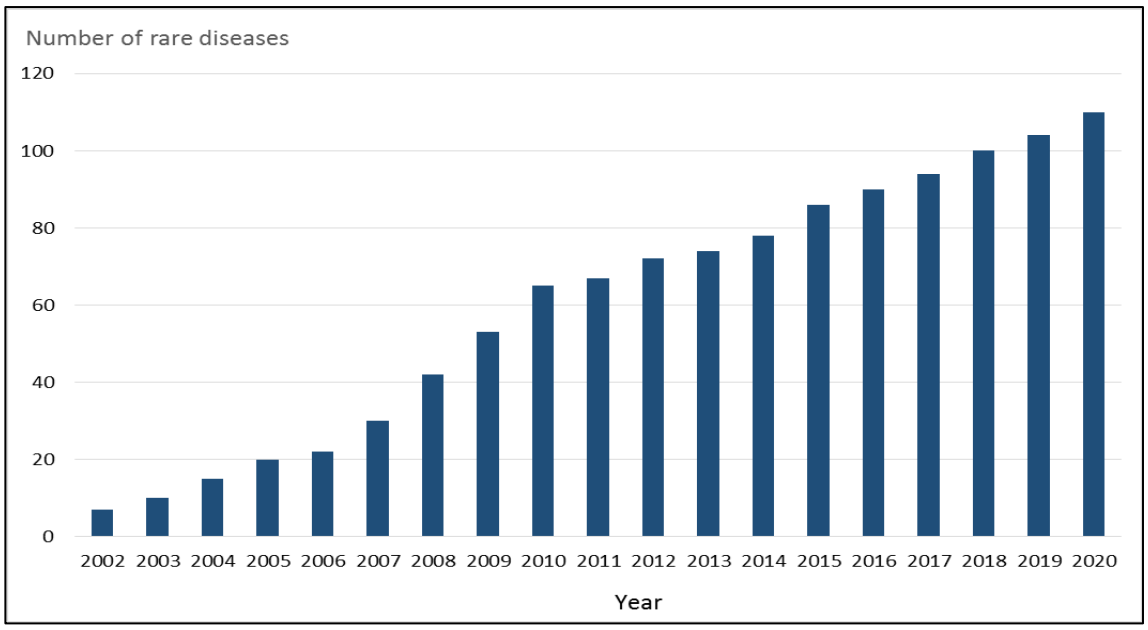

Figure 2.2 Cumulative rare diseases observed (2002-2010) and forecast (2011-2020) in Europe (Schey et al., 2011).

2.2.2 Issues of Rare Disease

The rare disease is seldom discussed among the public, especially laymen. These unfortunate patients often have inequality in distributing health care and are denied their right to get adequate treatment like those with other chronic diseases (Esquivel-Sada & Nguyen, 2018). In 2010, a survey of European Awareness of Rare Diseases (Special Eurobarometer 361) was conducted by TNS Opinion & Social and commissioned by the European Commission (TNS Opinion & Social, 2011). It showed that 63% of Europeans correctly defined rare diseases as diseases affecting a limited population and requiring particular care. However, some misunderstandings existed when 14% of respondents believed nobody could do anything or care about rare diseases. As the diseases are rare and sometimes extremely rare, some issues arose in dealing with rare diseases. Experts

and researchers have listed many issues or comments on patients' problems, as in Figure 2.3 (Forman et al., 2012).

Governance is a critical element in rare disease management. Due to the limited number of individuals affected by a rare disease, there is still a lack of government and regulatory bodies' action. One of the issues is the absence of proper coding specific to rare diseases used to diagnose and disease registry entry. A disease registry is vital in disease management to track the patients' clinical care, outcomes, safety, and comparative effectiveness. It is used to store individual personal information and their medical history for health policy purposes (Denis, Simoens, Fostier, Mergaert, & Cleemput, 2009; Gliklich, Dreyer, & Leavy, 2014). The Commission of European Communities also urges the establishment of registries and databases of rare diseases. They will be the primary mechanisms to increase knowledge of rare diseases and their management (Commission of The European Communities, 2008).

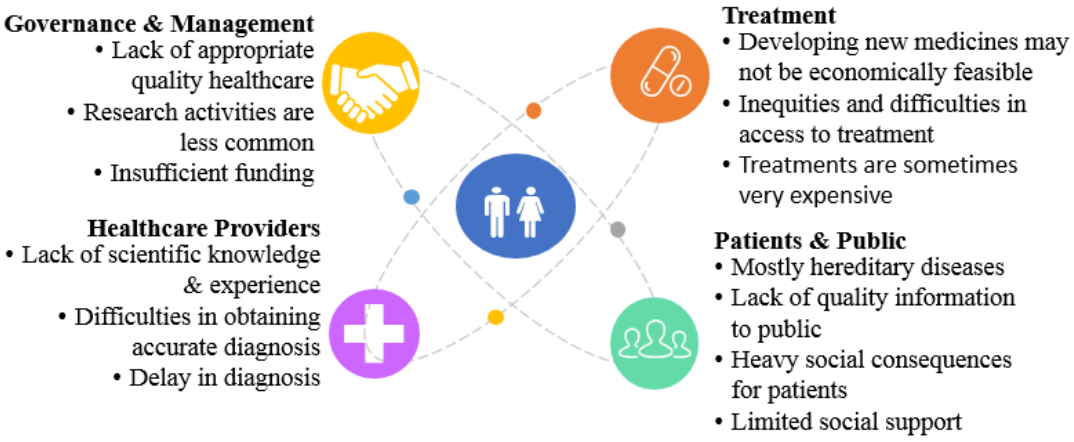

Figure 2.3 Issues associated with rare disease

The current International Classification of Diseases (ICD) system used in most countries does not have the same classification and coding for new rare diseases (Almalki, Alahmari, Guo, & Kelton, 2012; Song et al., 2012b). There are only about 500 codes specific to rare disease ICD-10 (Aymé et al., 2015; Bearryman;, 2015). As a result, encoding and registration of rare diseases are not possible. Thus, the WHO has recently released the ICD version 11 (ICD-11) in June 2018, which has listed 5,400 unique codes for rare diseases (Godsland, Samarasekera, & Lau, 2018). Besides Orphanet, which uses the European definition of rare disease, it also provides a unique and stable identifier called the ORPHA number to classify rare disease (Orphanet, 1997). Adopting international codes (ICD-11 and ORPHA number) for rare disease registries could improve the country's data-keeping and monitoring.

Lack of awareness and interest among medical professionals are the significant challenges faced by rare disease patients and families (Byrne, 2012). Many medical curricula do not provide sufficient time and training to healthcare professionals, which leads to a shortage of trained medical professionals in rare diseases. Due to a shortage or limited trained medical professionals in rare diseases, many believe they are unlikely to come across a rare disease in their professional careers (Byrne, 2012). Moreover, due to many types of rare diseases, medical professionals may not recognise each disease. The doctor will diagnose the condition based on their knowledge and experience or from published literature, registries, and others in the medical field. The lack of expertise and laboratory support services result in misdiagnosis and delayed diagnosis of rare conditions, giving the patients more risk (Almalki et al., 2012; Barham, 2012a; Lee & Thong, 2013).

There is no cure promised for most rare diseases. Very few have a specific and effective treatment (Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development, 2010). Some of the patients only need supplements for their deficiency. However, appropriate specific or symptomatic treatment and medical care plans can improve those affected qualities of life and may prolong their life expectancy (Orphanet, 2019). Whereas other medicine called "orphan drugs" only intend to treat a small population. It is harder to obtain than other conventional drugs, making the pharmaceutical industries hesitant to develop these orphan drugs under usual marketing conditions (Orphanet, 2019). The low prevalence makes it challenging to improve knowledge on treatments' safety and efficacy through proper studies. It is also due to a lack of motivation and economic incentive for manufacturers to develop drugs attributed to the small market (Seoane-Vazquez, Rodriguez-Monguio, Szeinbach, & Visaria, 2008). These weaknesses lead to orphan drugs being marketed at very high prices due to an absence of economies of scale in their sale. Since orphan drugs can be expensive and low on public health priority (low prevalence), they are often not reimbursable through the public fund. Hence, patients with rare diseases may appear marginalised as most of their treatment funding may be out of pocket. Other funding may come from public-private partnerships, charitable organisations, and industry groups (patient assistance programmes) (World Health Organization Regional Office for South-East Asia, 2008).

In reality, people with rare diseases miss out on treatments when primary policy focuses on other health challenges such as communicable and non-communicable chronic diseases (World Health Organization Regional Office for South-East Asia, 2008). There

are many different causes of rare diseases. Most rare disease patients have inherited genetic changes or chromosomes from their parents (Genetic and Rare Diseases Information Center, 2017). They are innocent and should give equal priority in getting treatment. Nevertheless, difficulty in diagnosis can be frustrating to patients and can cause financial implications to the families when facing difficulty finding specialised physicians (Hunter, 2005). Some of them have to see an average of 7.3 physicians before a confirmed diagnosis is made (Engel, Bagal, Broback, & Boice, 2013). In 2013, the Department of Health U.K. reported that four in every ten patients said they found it difficult to get a correct diagnosis (Department of Health UK, 2013a).

Rare disease patients and families are always facing difficulties in finding information about the rare disease. Because of the uncommon conditions, patients and family members cannot obtain enough information on their symptoms, prognosis, and treatment options from usual sources of health information from both primary and secondary health care providers (Lewis, Snyder, & Hyatt-Knorr, 2017). The lack of available clinical information provides patients and families with no choice but to become knowledgeable by themselves with help from patients' advocacy groups. On the other hand, this encourages patients and families to engage more actively in the group and their health decision making (Bratucu et al., 2014).

Given the current environment and complexities, there is a need to understand rare diseases in Malaysia, as they are seldom discussed among policy-makers and the public community. The discussion is often hampered by the lack or total absence of information on their epidemiology and burden. It is high time for Malaysia to take rare disease issues more seriously and offer suggestions on how to tackle rare diseases better, thus potentially

improving healthcare. Much is needed to be done, and it should start with understanding or creating awareness of what rare disease is in Malaysia.

2.3 Orphan Drug

2.3.1 Definition of orphan drug

Table 2.2 shows the definition of orphan drugs in six reference countries (Orphanet, 2019; Pacific Bridge Medical, 2017; U.S. Department of Health & Human Services). Orphan drug status does not mean that the FDA has approved the drug. However, sponsors must establish the safety and efficacy to treat a rare disease through adequate and well-controlled studies like other drugs (Center for Drug Evaluation and Research Small Business Assistance, 2012). Research and development are challenging and need a longer time for orphan drugs because of the small sample sizes to enrol a sufficient number of patients in clinical trials (Barham, 2012b; Denis et al., 2009). With the rarity of the disease and limited demand for treatment, many pharmaceutical companies are unlikely to develop and market orphan drugs unless there are incentives promised by the government (Rhee, 2015; Simoens, Cassiman, Dooms, & Picavet, 2012).

Many rare disease patients facing life-threatening or debilitating diseases are affected as early as a newborn. Without treatment, these patients' quality of life will be severely affected, and the impossibility to survive beyond adolescence. Rare disease patients deserve the same quality, safety and efficacy as other patients. Therefore, orphan drugs should also be submitted to the standard evaluation process (The European Parliament and of The Council, 2000). Reference countries such as the United States, the European Union and some parts of Asia, including Japan, South Korea, and Taiwan,

enacted legislation and regulation of rare diseases and orphan drugs (Song et al., 2012a). The establishment of this legislation and management allows the government to promote a few incentives, including financial subsidies, market exclusivity, tax credits, fee waivers, fast track approval, and protocol assistance (Table 2.3).

Table 2.2 Definition of orphan drug in six reference countries

Country	Definition of orphan drug
United States of America (U.S.A)	According to the Orphan Drug Act, the FDA classifies a pharmaceutical as an orphan drug if it treats a disease which: a) affects less than 200,000 people in the U.S., or b) affects more than 200,000 people in the U.S. but the cost of developing is not expected to be recovered from the drug sales
Europe Union (EU)	Orphan medicinal products are for: a) diagnosing, preventing or treating life-threatening or b) severe conditions that are rare and affect not more than 5 in 10,000 persons in the European Union (EU). c) Pharmaceutical companies are unwilling to develop products under normal market conditions, as the cost not be recovered by the expected sales of the products
Australia	A drug, vaccine or in vivo diagnostic agent is an orphan drug if it complies with this regulation. It: a) must be intended to treat, prevent or diagnose a rare disease; or b) must not be commercially viable to supply to treat, prevent or diagnose another disease or condition.
Japan	A drug considers as an orphan drug when: a) the drug is used to treat a rare disease or condition affecting less than 50,000 people in Japan b) the drug treats a disease or condition for which there are no other drugs/treatments available in Japan
South Korea	Orphan drug designation in Korea: a) less than 20,000 people in Korea suffer from the disease/condition, or b) there is no available treatment for the disease/condition
Taiwan	The Act defines orphan drugs as pharmaceuticals whose primary indication(s) is/are for the prevention, diagnosis and treatment of rare diseases (prevalence rate < 0.01% of the population: 1 in 10,000)

Table 2.3 Comparison of the regulation of orphan drugs in six reference countries

Items	United States	European Union	Australia	Japan	South Korea	Taiwan
Legal framework	Orphan Drug Act (1983), Rare Disease Act (2002)	Regulation (E.C.) No.141/2000 (1999)	Orphan Drug Policy (1997)	Revised orphan drug regulation (1993)	Orphan Drugs Guideline (2003)	Rare Disease Control and Orphan Drug Act (2000)
Administrative bodies involved	FDA / OOPD	EMA / COMP	TGA	MHLW	KFDA	DOH
Financial subsidies	Gov. grants for clinical research	Framework programs & national insurances	N	Gov. grants for clinical and non-clinical research	N	Gov. grants and awards from the central competent authority
Market exclusivity	7	10	5 (similar to other drugs)	10	6	10
Tax credits	Up to 50% for clinical expenses	Managed by member states	N	15% tax credits, up to 14% corporate tax reduction	N	N
Fast track approval	Yes	Yes (centralised approval)	Yes	Yes	N	Yes
Protocol assistance	Yes	Yes	Yes	Yes	N	Yes
Regulatory fee waives	Yes	Yes	Yes	Yes	N	N

Table 2.3 – Continued

Items	United States	European Union	Australia	Japan	South Korea	Taiwan
Pharmaceutical pricing	Market-driven	Depending on member states	Same as general drugs	Price negotiation	N	N
Medical expense reimbursement	Yes	Yes	Yes	For 56 diseases	Yes	70% -100% for low-income families
Public awareness	NORD	EURORDIS	AGSA	IDIC	KRDID, KORD	TFRD

N: no information; FDA: Food and Drug Administration; OOPD: Office of Orphan Products and Development; EMA: European Medicines Agency; COMP: Committee of Orphan Medicinal Products; TGA: Therapeutic Goods Administration; MHLW: Ministry of Health, Labour and Welfare; KFDA: Korean Food and Drug Administration; DOH: Department of Health; NORD: National Organisation for Rare Disorders; EURORDIS: European Organization for Rare Diseases; AGSA: Association of Genetic Support of Australia; IDIC: Intractable Disease Information Center; KRDID: Korean Rare Disease Information Database; KORD: Korean Organization for Rare Diseases; TFRD: Taiwan Foundation for Rare Disorders

2.3.2 Issues of orphan drug

Generally, there are many issues in dealing with rare disease treatment, from limited treatment or no specific treatment, inequalities, difficulties in access to treatment, lack of access to medications, high cost of treatment, until challenges to sustain the funding for treatment. One of the most significant issues of rare diseases is the high cost of therapy, specifically orphan drugs for certain rare diseases. Orphan drugs are often expensive and hardly meet cost-effectiveness for public reimbursement (Desser, Gyrd-Hansen, Olsen, Grepperud, & Kristiansen, 2010; M. Drummond & Towse, 2014; Iskrov, 2014). Picavet and colleagues (2011) concluded in a study in Belgium that awarding orphan drug designation status is associated with higher prices for rare disease indications (Picavet, Dooms, Cassiman, & Simoens, 2011). Reimbursement of orphan drugs is also an issue for decision-makers, legislators, health care professionals, industry leaders, families and patients. With increasing numbers of patients and new treatment with orphan drugs, governments remain concerned about the increased budget impact.

The current escalation in drug prices makes healthcare unaffordable for some rare disease patients. The pharmaceutical industry would often say that the high cost of drug development relative to the total market size to justify the high prices of orphan drugs (Fellows & Hollis, 2013; Gronde, Uyl-de Groot, & Pieters, 2017). With the increasing numbers of orphan drugs, governments are concerned about the future budget impact and cost-effectiveness compared to other healthcare interventions (Picavet, Cassiman, & Simoens, 2012). As healthcare is an essential component and a significant part of the government's expenditure, budgetary allocation and optimal use of available resources play a vital role in rare disease management.

Nowadays, the pricing of orphan drugs follows the same economic logic as in general. In essence, a manufacturer sets the prices to regain research and development costs and attain a particular profit margin. The manufacturers have a reason to charge the maximum amount for an orphan drug. Many researchers agree that prices of orphan drugs per treatment episode could be very high because of several potential reasons such as research and development cost, manufacturing and marketing cost, market exclusivity and profit for investigators and shareholders (Barak & Nandi, 2011; Denis et al., 2009). The high prices coupled with relatively sparse clinical data and associated complexity make a cost-effective case for the technology. Marketing exclusivity gives a monopoly to the manufacturer as no other company is allowed to market the orphan drug during the patent period. On the other hand, governments and decision-makers have limited negotiating power and often lack information about orphan drugs' cost structure (research, manufacturing, and marketing cost) (Hunter, 2005).

The governments are also under pressure from patient advocacy groups and media to accommodate new orphan drugs. As a result, health care payers are often forced to accept the price offered by the manufacturer. Some countries such as Greece, France, Italy and Portugal have a reference pricing system where companies must provide evidence-demonstrating cost-effectiveness versus current standards treatment to be considered for reimbursement (Godman et al., 2015). With these standards, the government monitors and initiates price cuts or discounts to keep pharmaceutical expenditure under control.

Some researchers have said that the high price has a limited impact on the total healthcare budget, as only a few patients have rare diseases. According to Drummond and

Hughes et al., the most challenging thing in an orphan drug study is to get a sufficient number of patients (M. F. Drummond, 2008; Hughes, Tunnage, & Yeo, 2005). Their inability to meet standard cost-effectiveness thresholds allows pharmaceutical industries to benefit from being categorised as orphan drugs. As a result, the long-term benefit projections are still hypothetical and painful to the decision-maker to list orphan drugs into formulary.

In modern medicines, economic evaluation and health technology assessment (HTA) are tools for health authorities and decision-makers to make decisions (Angelis, Lange, & Kanavos, 2018; The OECD Health Project, 2005). For orphan drugs, they are usually inhibited by limited and weak clinical data. (Iskrov, 2014). Uncertainty of evidence makes evaluators and regulators extremely cautious when appraising orphan drugs, especially allocating resources or reimbursement, which may lead to severe budget overspending. For these reasons, there is a need for a rational, clear, transparent and evidence-based approach towards pricing and reimbursement of orphan drugs (Simoens, 2011).

Over the past decades, several approaches have been developed, including evidence-based medicine, the burden of disease analyses, cost-effectiveness analyses, and equity analyses. However, it concentrates solely on single criteria and limited guidance to policy-makers in their choice of interventions. Moreover, they do not cover all the requirements that are relevant to governments and decision-makers. Whereas in reality, they need to make choices on interventions taking those criteria into account simultaneously. Drummond suggested using multi-criteria decision analysis (MCDA)

approaches, which consider additional factors to justify the high prices of most orphan drugs (M. Drummond & Towse, 2014).

The development of a multi-criteria approach to priority setting is necessary. It can shift away from existing health priority-setting tools that focus on single criteria towards transparent and systematic approaches that simultaneously consider all relevant measures (Baltussen & Niessen, 2006). Following these approaches, governments and other healthcare stakeholders, decision-makers would then discuss and decide on the weighting attributed to a few criteria as tools to evaluate new orphan drugs (Godman et al., 2015).

2.4 Policy and management of rare disease in the world

Helen Clark, the former administrator of the United Nations Development Programme, had stated in the 11th Annual International Conferences on Rare Diseases and Orphan Drugs. She said, "No country can claim to have achieved universal health coverage (UHC) if it has not adequately and equitably met the needs of those with rare diseases" (United Nations Development Programme, 2016). This statement triggered many countries to implement the UHC to handle rare diseases more seriously. A country must ensure the well-being of the people. With many issues and challenges in rare disease management, the governments should have a proper plan, strategy and actions towards total UHC achievement. The development of a national rare disease plan is crucial to ensure equal access to health care for these unfortunate patients.

Khosla and Valdez have compiled rare disease definitions, national plans, policies, and legislation on rare diseases from four regions around the globe (Khosla & Valdez, 2018). They reported the similarities and differences among law-based national

approaches on rare diseases in Table 2.4 and Figure 2.4. From 23 countries, the Europe region presented the most unified legislation in which all eight countries adopted the same rare disease definition and developed national plans, laws and programs or strategies. However, none of the other countries has developed a national policy for rare diseases. The definition of rare disease also varies among countries even though within the same region. Thus, creating another hurdle to the states towards the integration of rare disease plans internationally. Nevertheless, each country has its policies, regulations, programmes, or procedures in developing rare diseases management, access to treatment or orphan drugs, screening, and others.

Table 2.4 Rare disease definitions, plans, legislations, programs and strategies of countries in four regions

Region/ Country	Definition of rare disease	National plan	Legislation	Program or strategy	Highlights
Region: Canada and the United States					
Canada	Fewer than 5 cases per 10,000 people	No	No	Yes	Health Canada's Special Access Program Orphan Drug Framework The Canadian Organization for Rare Disorders (CORD) 5 Strategic Goals for Canada's Rare Disease Strategy
United States	Fewer than 200,000 cases	No	Yes	Yes	Orphan Drug Act (1983) Rare Disease Act (2002) National Institute of Health Research Programs

Table 2.4 - Continued

Region/ Country	Definition of rare disease	National plan	Legislation	Program or strategy	Highlights
Region: Europe (8 countries)					
Bulgaria	Fewer than 5 cases per 10,000 people	Yes	Yes	Yes	National Plan (2009-2013)
France	Fewer than 5 cases per 10,000 people	Yes	Yes	Yes	First National Plan (2005-2008) Second National Plan (2011-2014)
Germany	Fewer than 5 cases per 10,000 people	Yes	Yes	Yes	Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen" (NAMSE)
Greece	Fewer than 5 cases per 10,000 people	Yes	Yes	Yes	National Plan (2008-2012)
Italy	Fewer than 5 cases per 10,000 people	Yes (draft)	Yes	Yes	Ministerial Decree n. 279/2001

Table 2.4 - Continued

Region/ Country	Definition of rare disease	National plan	Legislation	Program or strategy	Highlights
Portugal	Fewer than 5 cases per 10,000 people	Yes	Yes	Yes	National Plan (2008-2015)
Spain	Fewer than 5 cases per 10,000 people	Yes	Yes	Yes	National Plan (2010)
United Kingdom	Fewer than 5 cases per 10,000 people	Yes	Yes	Yes	U.K. strategy for rare disease
Region: Asia Pacific (7 countries)					
Australia	Fewer than 2,000 cases.	No	Yes	Yes	Orphan Drug Program (1998)
China	1 case per 500,000 people.	No	No	Yes	China pilot project Rare Disease Clinical Cohort Study
Japan	Fewer than 50,000 cases	No	Yes	Yes	Pharmaceutical Affairs Law (1993) Revision of Measures to Combat Diseases Specified Disease Treatment Program