COST-EFFECTIVENESS ANALYSIS OF IDURSULFASE FOR THE TREATMENT OF HUNTER SYNDROME IN A TERTIARY REFERRAL CENTRE FOR RARE DISEASES IN MALAYSIA: A PARTITIONED SURVIVAL MODEL APPROACH

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by

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LIST OF DEFINITIONS

Clinical study	clinical study is defined as a clinical trial investigating one or more interventions or an observational study (prospective or cross-sectional) in a routine clinical practice setting.
EFS	Event-free survival. The time between treatment and having a specific 'event' such as hearing impairment.
Health utility	A representation of the strength of preference for a given health-related outcome on a cardinal numeric scale. In this scale, a value of 1.0 represents full health, while 0 represents a state of being deceased. Additionally, negative values on this scale represent states worse than being deceased (Powell et al., 2022).
HRQoL	Health-related quality of life. A multi-dimensional concept that represents the patient's subjective, general perception of the impact of a disease and its consequent therapy on daily life, physical, psychological, and social functioning, and well-being (Chung et al., 2022).
HSU	Health-state utility. The estimate of the health utility for a given health state. For this study, this refers to the health-utility estimate for an economic model health state.
Mapping	The development and use of an algorithm (or algorithms) to predict HSUVs through regression analysis using data from an indicator or measures of health (Ara et al., 2017; Meregaglia et al., 2022).
OS	Overall survival. A key endpoint in oncology in the advanced/metastatic setting is defined in a trial setting as the time from randomisation (or study entry for non-randomised studies) to death from any cause.
PBM	Preference-based measure. A measure of health utility is a measurement system that allows patients to describe the impact of ill health. It assigns a utility score to these descriptions based on people's preferences for health states (Wolowacz et al., 2016). These measurement systems consist of two components: • A standardised descriptive system for health or its impact on HRQoL (sometimes referred to as a multi-attribute utility instrument). This system comprises several multi-level dimensions that describe a universe of health states. • An algorithm for assigning utilities to each health state described by the system (often described as a value set). Algorithms have been based on various valuation methods, such as time trade-off, standard gamble, and discrete-choice experiments (Robinson et al., 2006).

PFS	Progression-free survival. Defined as the time from randomisation to progression or death (whichever occurs first), it has therefore been suggested as a potential surrogate for OS in advanced cancer; this usually requires much shorter follow-up than OS.
Survival analysis	Described by Collet et al. (2015) as *"the analysis of data in the form of times from a well-defined time origin until the occurrence of some particular event or endpoint".*

LIST OF ABBREVIATIONS

AFT	Accelerated failure time
AIC	Akaike Information Criterion
AUC	Area under the curve
BIC	Bayesian Information Criterion
CBA	Cost-benefit Analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CUA	Cost-utility Analysis
DALY	Disability-adjusted life-year
EFS	Event free survival
HCP	Healthcare professional
HOS	Hunter Outcome Survey
HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly Specialised Technology
HSUV	Health state utility value
HSV	Health state value
HTA	Health Technology Assessment
HUV	Health utility value
ICA	Indirect care activity
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
KM	Kaplan Meier
MoH	Ministry of Health (Malaysia)
MRDS	Malaysian Rare Disease Society
NICE	National Institute for Health and Care Excellence
OD	Orphan drug
On Costs	Salary on costs
OS	Overall survival
PFS	Progression-free survival
RD	Rare disease
SEV	Subjective evaluation
SMA	Spinal muscular atrophy
UHC	Universal healthcare
TA	Technology assessment

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ANALISIS KEBERKESANAN KOS IDURSULFASE BAGI RAWATAN SINDROM HUNTER DI PUSAT RUJUKAN TERTIARI PENYAKIT JARANG JUMPA DI MALAYSIA: SATU PENDEKATAN MODEL PEMBAHAGIAN KELANGSUNGAN HIDUP

ABSTRAK

Sindrom Hunter (MPS-II) adalah antara keadaan genetik jangka hayat panjang paling berkos tinggi yang dikaitkan dengan bebanan penyakit yang berat dan memberikan kesan yang signifikan terhadap keluarga, sistem kesihatan, dan masyarakat Malaysia. Lebih banyak kajian yang diperlukan bagi menunjukkan nilai wang dari perspektif masyarakat dengan mengambil kira maklumat keberkesanan jangka masa panjang, situasi kos setempat, dan nilai utiliti kesihatan penduduk di Malaysia. Satu pedekatan analisis pembahagian empat keadaan kelangsungan hidup de novo telah digunakan untuk meramal dan membandingkan kos, QALYs, dan nisbah keberkesanan kos tambahan bagi dua model penjagaan iaitu rawatan penggantian enzim idursulfase (ERTI) dan rawatan standard (SOC) untuk sepanjang hayat dari perspektif masyarakat. Analisis menunjukkan jangka hayat yang lebih panjang dalam kumpulan ERTI berbanding kumpulan SOC, dengan pesakit SOC secara puratanya tidak mampu hidup melebihi dekad kedua dalam satu tempoh kehidupan. Sebaliknya, jangka hayat kumpulan ERTI mampu melebihi tempoh 20 tahun [95% Sela Keyakinan (SK), 19.02-20.70]. Pertambahan QALYs bagi seumur hidup adalah 4.1 tahun (2.37-5.68). Kos tambahan dianggarkan berjumlah RM12 juta (95% SK, 11.4 juta-12.6 juta), yang hampir keseluruhannya terdiri daripada kos ubat (99%). Kos pertambahan setiap unit QALY dianggarkan kira-kira RM3 juta (95% SK, 2.2 juta-4.8 juta). Analisis kepekaan menunjukkan bahawa pendorong utama ICER / ICUR adalah kualiti hidup

dalam keadaan pra-progresif dan bukan selepas keadaan progresif, pendekatan kadar diskaun yang berbeza selain daripada kos perolehan ERTI. ICERs / ICURs berada di luar ambang batas piawai kos-keberkesanan yang biasa digunakan dalam semua keadaan analisis. Pada harga semasa, idursulfase tidak memenuhi ambang batas piawai kos-keberkesanan di Malaysia. Walaupun tinggi, ICER untuk MPS-II adalah setara dengan penyakit jarang jumpa lain yang dirawat dengan ERT. Penemuan ini menggambarkan kesulitan pelaksanaan analisis kos-keberkesanan penyakit jarang jumpa yang belum diterokai ini dan potensi cabaran dalam menyediakan akses pesakit kepada ubat tanpa paten.

COST-EFFECTIVENESS ANALYSIS OF IDURSULFASE FOR THE TREATMENT OF HUNTER SYNDROME IN A TERTIARY REFERRAL CENTRE FOR RARE DISEASES IN MALAYSIA: A PARTITIONED SURVIVAL MODEL APPROACH

ABSTRACT

Hunter syndrome (MPS-II) is among the costliest life-long genetic conditions associated with a substantial burden of illness and its significant impact on Malaysia's health systems, families, and society. There needs to be more studies demonstrating its value for money incorporating long-term effectiveness data, local costs situation, and population-specific utility values. The objective is to estimate the cost-effectiveness of long-term enzyme replacement therapy of idursulfase (ERTI) versus standard-of-care (SOC) from a societal using a streamlined modelling strategy in R. A de novo four states partitioned survival model approach was utilised to project and compare lifetime costs, QALYs, and incremental cost-effectiveness ratios of two care models. The disease progression was based on independent survival modelling of relevant published Kaplan-Meier (KM) data. The healthcare and out-of-pocket costs were drawn from the local setting. The quality-of-life was measured using the EQ5D5L and the TTO valuation of health state vignettes that matches the states in the model. Probabilistic and deterministic sensitivity analyses were conducted to test the uncertainty around the model results. The life expectancy was significantly longer in the ERTI than in the SOC, with SOC patients not surviving beyond the second decade of life on average. In contrast, life expectancy in the ERTI group exceeded 20 years (95% CI, 19.02-20.70). The lifetime incremental QALYs were 4.1 years (2.37-5.68). Incremental costs were estimated to be RM12 million (95% CI, 11.4 million-12.6

million), which primarily consisted of drug costs (99%). The incremental costs per QALY were estimated to be approximately RM3 million (95% CI, 2.2 million-4.8 million). Sensitivity analyses showed that the key drivers of ICER/ ICUR were quality-of-life in the pre-progression state and not the post-progressive state, differential discounting approach besides the acquisition cost of ERTI. The ICERs/ ICURs were beyond any conventionally used cost-effectiveness threshold in all cases. At its current price, idursulfase does not meet traditional cost-effectiveness thresholds in Malaysia. Although high, the ICER for MPS-II was comparable to other RDs treated with ERT.

CHAPTER 1

INTRODUCTION

Rare diseases (RDs) often characterised by their low prevalence, present unique challenges to healthcare systems worldwide. While rare, these diseases collectively affect a significant portion of the global population. The rarity and complexity of these conditions often result in a lack of understanding, leading to delayed diagnosis, limited treatment options, and significant economic burden. Patients with RDs and their families face many challenges. As these conditions are often debilitating and chronic, they pose considerable long-term psychological, medical and financial burdens on the patient and their parents, siblings and extended family (Chu et al., 2022). The complexity of rare diseases is multifaceted, encompassing diagnostic challenges, limited treatment options, economic implications, and the need for specialised care.

Mucopolysaccharidosis type II (MPS-II), or Hunter syndrome, is a rare lysosomal storage disease and life-debilitating metabolic disease (Burton et al., 2023). MPS-II represents the majority (N=30/79) of mucopolysaccharidosis type of family disease in Malaysia, according to data from the National Referral Centre of the Genetics Department (Ngu, 2018). This condition arises from a deficiency in the lysosomal enzyme iduronate-2-sulphatase (I2S) due to mutations in the IDS gene, accumulating glycosaminoglycans in various tissues and organs. The accumulation results in multiple symptoms, including skeletal deformities, cardiovascular complications, and cognitive impairments (D'Avanzo et al., 2020). The management and treatment of MPS-II have evolved over the years from being limited to supportive care and consisting of surgery to emergent new treatments such as

enzyme replacement therapy of idursulfase (ERTI). These pharmacological treatments for the RDs, termed ‘orphan drugs’ (ODs), are often life-changing but are limited to a selected number of RDs. ERTI emerged over a decade ago as the only promising treatment option, offering potential improvements in life expectancy and quality of life for MPS-II patients (Solano et al., 2020). However, the ERTI is listed as the world's top ten most expensive drugs, putting it out of reach for most patients to afford privately (Giugliani et al., 2019). Moreover, the high costs associated with ERTI and the challenges of assessing its long-term efficacy and cost-effectiveness have raised concerns among healthcare policymakers and stakeholders in the government-funded healthcare system (A. Santos et al., 2018).

Economic evaluations (EE) play a crucial role in informing healthcare decisions, especially in the context of RDs, where resources are limited and the costs of treatments are extremely high. Cost-utility analysis (CUA), a subtype of economic evaluation, has been employed to assess the value of interventions by comparing the costs to their health outcomes (consequences), typically measured in quality-adjusted life years (QALYs) to ensure efficient choice while using the minimal costs (Nicod et al., 2021). As the ERTI needs to be used for an extended period, the CUA represents a valuable criterion for evaluating its long-term value and inform resource allocation decisions. However, conducting CUAs for RDs like MPS-II presents unique challenges due to the scarcity of data and the inherent uncertainties associated with long-term effectiveness projections (Postma et al., 2022).

Technological advancements and data analytics have given researchers new tools to address these challenges in recent years. The R programming language, for instance, offers a ‘flexible’ platform for health decision analysis in the form of health economic modelling, allowing for integrating published data sources (Guyot et al.,

2012) and applying the latest statistical techniques (Incerti et al., 2019) in a validated environment. Such tools can enhance the reliability and transparency of EE results, ensuring that they provide reliable and rigorous methodologies for decision-makers (R. Smith et al., 2020).

Despite these advancements, significant gaps remain in our understanding of the cost-effectiveness of treatments for MPS-II, especially in the context of different healthcare systems and economic environments. There is a pressing need for comprehensive EE that considers the clinical and economic aspects of MPS-II treatments, considering the unique challenges and opportunities of RDs (Paracha et al., 2022). By leveraging the capabilities of the R programming language and drawing on a wide range of data sources, this research seeks to offer valuable insights for healthcare policymakers, clinicians, and other stakeholders involved in the management of MPS-II and other RDs in Malaysia (Shafie et al., 2020).

1.1 Rare diseases characteristics

The World Health Organisation (WHO) characterises RDs, or orphan diseases, as conditions that affect a small proportion of the general population (Chuah et al., 2018). While the individual disease is uncommon, the cumulative number of diagnosed RDs is between 7,000 and 8,000, affecting approximately 3.5-5.9% of the worldwide population, equating to an estimated 263-446 million individuals globally (Chung et al., 2022). These conditions are typically chronic, progressive, and debilitating, resulting in substantial morbidity and mortality. Approximately 80% of them are genetic disorders affecting young children, and the remainder are rare cancers, autoimmune diseases, congenital malformations, and the rare manifestation

of common diseases. Together, they represent many patients who encounter common issues from lengthy and complex diagnostic journeys to limited and expensive treatment options (EURORDIS, 2009). These effects extend beyond just the patient, impacting family members and caregivers, thus broadening RD influence to around 1.05-1.4 billion individuals globally (Chung et al., 2022). Unfortunately, these patients are at risk of missing life-saving treatment due to lack of understanding and diagnostic difficulties from healthcare providers (HCPs), health system leaders, and health policymakers (Shafie et al., 2020). Tragically, around 30% of individuals impacted by RDs die before age five (Song et al., 2012). The issue stems from gaps in disease knowledge among HCPs, diagnostic difficulties, and high treatment costs (Cai et al., 2019).

Around 9%, or 45 million individuals in Southeast Asia suffer from RDs (Right Diagnosis, 2015). Notable examples of RDs in Malaysia include lysosomal storage diseases (LSD) such as Fabry, Pompe, and Mucopolysaccharidosis. Blood diseases like haemophilia, bone disorders like achondroplasia, and adult-onset diseases like Huntington's disease and motor neuron disease are all considered RD (Ngu, 2018). The exact number of patients with RDs in Malaysia is unknown, as many RDs may not be adequately diagnosed or reported. However, it is estimated that approximately 6-8% of the population, or about 3 million to 4 million people, are affected by RDs in Malaysia. The tiny percentage of the affected population varies according to the disease type and definition. According to Ferreira (2019), about 6% of today’s population is affected by rare diseases. Malaysia lacks official estimates on the number of patients with rare diseases and does not adopt an epidemiological definition (Silva et al., 2015). WHO defines RD as 0.65 to 1 in 100,000 population

(Shafie, 2019), and Malaysia has unofficially adopted the Malaysia Rare Diseases Society (MRDS) definition of 1 in 4000 (Shafie et al., 2020).

RDs present significant challenges in Malaysia due to various gaps and deficiencies in diagnosis and care. Collectively, they affect a substantial portion of the population but individually have a low prevalence that contributes to underdiagnosis and late identification. Awareness is limited among healthcare professionals and the general public, while expertise and newborn screening are scarce. As a result, diagnoses are often delayed, and many children suffer complications. Treatment options frequently remain unavailable or must be self-funded, burdening families financially. No centralised national policy or registry coordinating rare disease management remains fragmented across primary and secondary health facilities. While genetic disorders constitute a significant cause of paediatric hospitalizations, specific expertise and long-term needs are often unmet partly due to the complexity of the RDs (Elliott et al., 2020). Without concerted efforts to establish specialised centres, expand screening programs, and ensure affordable therapies through a national plan, the impacts on health outcomes, patient quality of life, costs, and equity will likely continue to worsen (Shafie et al., 2016; Chuah et al., 2018; Thong et al., 2019; Shafie et al., 2020).

1.2 Overview of MPS-II

Mucopolysaccharidoses (MPSs) are a group of rare lysosomal storage diseases caused by different enzyme deficiencies. These deficiencies lead to glycosaminoglycans (GAGs) accumulation in lysosomes and the extracellular matrix, resulting in storage-induced inflammation. The build-up in organs and tissues leads

to cell damage or abnormalities, particularly affecting how cells function, contributing to MPS symptoms (Sato et al., 2020). The toll-like receptor-4 (TLR4) pathway, upregulated by the accumulation of heparan sulfate, is mainly involved in MPS types I, II, VII and III. At present, eleven discrete subcategories of MPS exist, each correlating to a specific lysosomal enzyme deficiency: MPS I (Hurler, Hurler-Scheie, and Scheie syndromes), MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome, with subtypes IIIA, IIIB, IIIC, and IIID), MPS IV (Morquio syndrome, with subtypes IVA and IVB), MPS VI (Maroteaux-Lamy syndrome), MPS VII (Sly syndrome), and MPS IX. All types of MPS exhibit autosomal recessive except MPS-II, which is an X-linked disorder and thus predominantly affects males. If both parents are carriers, there is a 25% chance of having an affected child for all types of MPS with each pregnancy. In contrast, there is a 50% chance of having an affected son with each pregnancy for MPS-II. A similar disease has recently been discovered in a bird species (Jolly et al., 2021).

Although MPS-II is an X-linked recessive condition, rare sporadic female cases have been reported (Sestito et al., 2015). The condition of MPS-II arises from a deficiency in the lysosomal enzyme iduronate-2-sulphatase (I2S) due to mutations in the IDS gene. The absence or malfunction of this enzyme leads to the accumulation of glycosaminoglycans (GAGs) in various organs and tissues, including the liver, spleen, heart, bones, joints, and respiratory tract. This accumulation disrupts cellular functions, resulting in a spectrum of multisystemic disease manifestations. As a result of accumulation, patients experience progressive somatic disease manifestations including coarse facial features and skeletal pathology such as claw-like hands and stiff joints, short stature, birthmarks (often referred to as Mongolian spots), developmental delays, hepatosplenomegaly, hearing abnormalities, and the presence

of inguinal or umbilical hernias, although progression may be slower in individuals without cognitive impairment (R. Martin et al., 2008; Muenzer et al., 2009; Keilmann et al., 2012; Wooten et al., 2013; H.-Y. Lin et al., 2016; H.-Y. Lin et al., 2018). Cardiac manifestations are also prevalent, with valve abnormalities being the most common. Specifically, mitral and tricuspid valve regurgitation is observed in approximately 71.9% of patients, while aortic and pulmonary valve regurgitation is seen in about 36.8% (Hoffmann et al., 2011; Sohn et al., 2012). The skeletal muscle, respiratory, and heart are primarily affected, leading to death from respiratory and cardiac failures.

The clinical presentation of MPS II varies among patients with high genetic heterogeneity. Patients of severe form display progressive central nervous system (CNS) involvement, impacting their intellectual functions and normal daily behaviour. Severely affected patients may survive until the second decade of life, whereas less severe patients typically can survive into adulthood (Cohn et al., 2013). Although the disease is classified into “mild” or “severe” based on clinical severity and the progressiveness of CNS that results in severe cognitive impairment, MPS-II should be considered as a spectrum between two extreme forms of the disease. The progression of MPS-II is characterised by a series of escalating somatic symptoms affecting multiple organ systems as the patient ages, with variable characteristics and no specific pattern or broad spectrum of clinical manifestations (Muenzer et al., 2017; Mungai et al., 2021). Patients typically present in early childhood with or without progressive cognitive decline, skeletal abnormalities, hearing and vision loss and cardiovascular or respiratory complications (Cohn et al., 2013; Giugliani et al., 2020). The condition is progressive and severely debilitating without treatment, with a median survival of 12-14 years (Decker et al., 2017).

Alternatively, MPS-II is regarded as a progressive disease that evolves through three phases: musculoskeletal, respiratory, and cardio-respiratory stages (Coyle et al., 2013; Winquist et al., 2014). The initial stable phase, during which the disease is stable and does not progress (Guffon et al., 2015), is followed after a variable interval by progression through an accelerated phase to a slowly progressive ventilated state (H. Y. Lin et al., 2019).

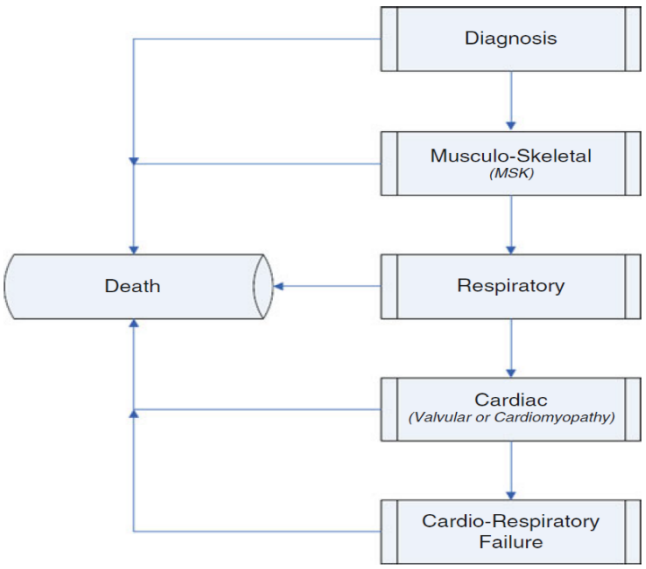

Figure 1.1 Progression of MPS- II as suggested by Coyle et al., (2013)

The management is challenging and requires a long-term multidisciplinary approach (Muenzer et al., 2021). Of interest is the significant social burden on families that comes with weekly in-hospital treatment, including adversely affecting parental employment in all but one family and 20% loss of the schooling week for the child. This is a particular concern considering the educational challenges most of these children already face. The weekly commitment to treatment has resulted in adverse psychosocial effects, as seen by some parents, for the child, siblings and parents themselves. Nevertheless, all the parents reported the positive impact of

treatment on their child and felt the treatment's benefits outweighed the burden involved. (Buraczewska et al., 2013).

The literature highlighted the significant social burden and management of rare diseases like MPS-II places on families. This includes the weekly commitments required for in-hospital treatment like enzyme replacement therapy (ERT) that can adversely impact parental employment and children's education. A recent study by (Chu et al., 2022) explored gender differences in the burden of informal caregiving for rare disease patients. The study found that mothers took on most care responsibilities, such as administering treatments, coordinating appointments, and providing emotional support. Fathers were more likely to support financially and assist with transportation but were less involved in direct care activities. The additional care workload disproportionately affecting working mothers can exacerbate the negative psychosocial impacts reported by some families. Recognition of these gender aspects in valuations from a societal perspective is important to capture the full spectrum of rare disease impacts more comprehensively on caregivers and help allocate support services accordingly.

Diagnosis of MPS-II is multifaceted, involving an assessment of clinical features, biochemical parameters, and molecular characteristics. Approximately 90% of patients were diagnosed during the chronic non-progressive phase of the disease (Hoyle, Rogers, et al., 2011). Since the ERT is the only treatment available, it requires regular monitoring by an interdisciplinary team across various specialists to ensure optimal patient care. Notably, an increasing number of MPS-II patients are reaching adulthood, emphasizing the importance of a smooth transition of patient care management approach from paediatric to adult.

1.3 Enzyme Replacement Therapy of Idursulfase

The disease-specific therapies for MPS disorders include ERT and hematopoietic stem cell transplantation (HSCT). These treatments are available for MPS-I, II, VI, and VII (Clarke et al., 2012). ERT provides a functional enzyme to digest GAG storage in lysosomes, reducing tissue accumulation and slowing clinical progression (Clarke et al., 2012). The only treatment for MPS-II is enzyme replacement therapy with idursulfase (ERTI) using recombinant human iduronate-2-sulfatase (Wraith, Beck, et al., 2008). Although these treatments cannot cure the diseases, they can improve or alleviate the comprehension of the disease and significantly impact the progression of the MPS-II disease (Ngu, 2018). If treated early, ERTI can slow the progression of the disease and has been attributed to the increase in the long-term survival outcome in treated patients (Burton et al., 2017).

ERTI is well tolerated and was found to reduce GAG excretion and positively affect hepatosplenomegaly and respiratory manifestations. Comparable to other studies, no effect was seen on the central nervous system or cardiac manifestations of MPS-II (Solano et al., 2020). The treatment is currently administered intravenously and does not cross the blood-brain barrier. Also, the GAG accumulation and resultant valve deformation appear to progress despite ERTI. Several clinical trials have demonstrated that idursulfase therapy slows disease progression, improves endurance pulmonary and joint function, decreases spleen and liver size and stabilizes renal function when initiated as early as 6 years old (Muenzer et al., 2011). Previously, it was not yet known whether the progression of an irreversible change of valvular disease might be slowed by early and long-term ERTI (Hoffmann et al., 2011). However, current evidence showed that the prevalence of mitre valve involvement in overall valvular disease progression is increased by 15% and 40% of patients,

respectively (Muenzer et al., 2021). In contrast, ERTI improves distance walked in six minutes (6MWD), but the average improvement is less than 10% above baseline values (CEDAC, 2017).

While ERTI has been shown to stabilize some manifestations of the MPS-II based on clinical trials, there remain significant uncertainties regarding its longer-term effectiveness and magnitude of quality-of-life benefits. Administration of idursulfase therapy requires weekly infusions in-hospital or at specialised clinics, placing substantial treatment burdens on patients and their caregivers. However, the clinical improvements achieved have been modest. For instance, the 6-minute walk distances are increased on average less than 10% above baseline. More importantly, idursulfase has not demonstrated improvements in quality of life, reduced rates of hospitalization, or decreased need for home care support, which are arguably more clinically meaningful outcomes for patients (da Silva et al., 2016; CEDAC, 2017). At an annual drug cost of over $ 650,000 (CEDAC, 2017), € 600,000(Kanters et al., 2013) and RM 700,000 (Shafie et al., 2020) per patient in the US, Netherlands and Malaysia respectively, many have questioned whether ERT provides good value for money given this lack of robust evidence demonstrating benefits in important domains like daily living functioning and well-being. Ongoing research incorporating the long-term real-world effectiveness data is still needed to fully assess the quality and effectiveness of outcomes delivered by the idursulfase over the patient's life-long treatment to the overall healthcare systems resources. Nonetheless, the life expectancy of MPS-II patients has positively increased since the introduction of ERTI (Burton et al., 2017; Broomfield et al., 2020).

1.4 Treatment Management Models

As RD emerges as a global health priority, an integrative model of patient-centred and multidisciplinary care across primary, secondary, and tertiary levels is required for comprehensive genetic management (Chung et al., 2022). For instance, the National Health Service (NHS) in the United Kingdom has specifically structured 'Specialist Services' to handle complex or low-prevalence 'ultra-rare' conditions like MPS-II (NHS, 2021). Referral pathways funnel patients to regional centres of expertise where specialised multidisciplinary teams provide a coordinated approach to evaluate the effectiveness of long-term care through a specialised or single technology assessment report (NICE, 2018).

Similarly, Canada has established a network of 16 provincial resource centres focused on diagnosing and treating specific RD groups, including lysosomal storage disorders (CCSNE, 2022). Patients are triaged through primary care and seen by nephrologists, neurologists, or other specialists with genetic disease experience. Comparatively, the fragmented U.S. healthcare system presents challenges for coordinated RD care (Biesecker, 2009). However, patients can potentially leverage a 'medical home' model facilitated through participating in comprehensive care centres as implemented by the NIH's Rare Diseases Clinical Research Network (RDCRN, 2022).

Malaysia has a parallel public-private healthcare system. The Ministry of Health (MoH) regulates both sectors and is the largest public healthcare provider (Barber et al., 2019). The MoH was aware of the rising costs of healthcare funding and the need for coordinated care provision and treatment access for RDs. Steps have been taken to mobilise other health funding sources to improve access to RD treatment. However, access to such therapies often exist is often restricted due to

high costs and perceived limited benefits for a smaller patient population, creating a challenge for those affected RDs to receive appropriate treatment. One of the suggested remedies is to use a trust fund in conjunction with tax incentives to leverage private sector and charitable support (Thong et al., 2019). In 2015, idursulfase was approved in the country, but there were obstacles to the treatment due to high costs and lack of specialised centres (Zulkifli et al., 2018). In order to cover the ongoing costs of enzyme therapy (ERT) for approved indications of rare diseases, such as MPS-II, the Enzyme Therapy Patient Fund was established in 2018 (ETPF, 2022). However, the lack dedicated national centres for rare disease in many developing countries presents difficulties for prompt diagnosis, treatment access, and care coordination (Zurynski et al., 2017).

As a middle-income country, Malaysia has established several tertiary hospitals as regional referral centres to improve the management of rare disease (Ngu, 2018). The standard of care (SOC) for managing MPS-II includes a multidisciplinary approach, including supportive care, and symptom management (Krishnan et al., 2021). Supportive care focuses on managing clinical manifestations such as orthopaedic issues, cardiac and respiratory problems, ear infections, and respiratory infections has positively improved patient morbidity over the years (Jezela-Stanek et al., 2020). Recently, significant progress in achieving universal health coverage and the formation of metabolic clinics in major hospitals have made access to medicines and centralised care for the needs of patient with rare disease a reality (Taruscio et al., 2013).

1.4.1 Monitoring of Enzyme Therapy Response

In Malaysia, RDs patients are managed by a tertiary referral genetic unit in Kuala Lumpur Hospital. Geneticists, paediatricians, genetic counsellors, and nurses are the front-line providers of medical genetics services in the country (Shafie et al., 2020). This involves the administration of infusion in the clinics by specialised metabolic physicians and genetic nursing staff (Fasanmade et al., 2013). Nurses remain the highest personnel resources employed by the Ministry of Health (MOH) in the labour force (Pathamathan, 2015).

In today's economic climate, the HCP must constantly perform at the highest level by re-evaluating their quality of care. As a result, there is considerable interest in measuring the health personnel activities and workload via professional judgment or subjective evaluation (Twigg et al., 2009), clinical work indicators (or productivity data) (Baernholdt et al., 2010), and time and motion study (TMS). In recent years, outpatient genetic care has played a significant component in medical genetic management (Cai et al., 2019). However, there have been no works published so far to the best of the author's knowledge about the work activity of genetic nurses and pharmacists in comparison to geneticists (McPherson et al., 2008) and genetic counsellors (Heald et al., 2016; Attard et al., 2019).

The primary care model provides comprehensive multidisciplinary care but incurs higher overhead patient care costs. Alternatively, the shared-care model involves decentralizing infusions to local hospitals closer to the patient's residential area for home infusion therapy management in coordination with the specialist referral centre under a periodic review system (Burton et al., 2011; Sestito et al., 2015). The strategy reduces patient travel distances while utilizing community healthcare resources more efficiently and enhances patient compliance (Buraczewska

et al., 2013). Thus, there is an obvious need to comprehend and disseminate information regarding their progressive role as the patient's primary point of contact in this largely unexplored area of RDs. Moreover, ERT places a lifelong financial and logistical burden as it requires intravenous infusions every week administered in a clinic setting under specialised healthcare staff supervision (Sestito et al., 2015). The tertiary centre retains management of complex cases or during infusions in the initial stabilisation phase. Insurance coverage under the National Health Protection Scheme (JKN) introduced in 2019 pays for ERT and supportive care for eligible rare disease patients, reducing out-of-pocket costs substantially (Cheah, 2020). Nonetheless, ERT remains a major budgetary component challenging the optimisation of limited healthcare spending.

1.4.2 Limited Healthcare Resources

Limited resources and endless demands for their use create a complex competing interest in healthcare. These resources include people, time, facilities, equipment, and knowledge (Drummond et al., 2015). Health economics is a tool for understanding how best to allocate these scarce resources. Pressures on healthcare budgets have led to the growing importance of Health Technology Assessment (HTA) in the Asia-Pacific region, including the Health Technology Assessment Section (MaHTAS) in Malaysia. This shows the growing recognition of evidence-based policy making for resource allocation (Mohd Darus et al., 2010). MaHTAS, alongside the Formulary and Pharmacoeconomic Unit in the Pharmaceutical Services Division (PSD), aims to ensure the sensible use of healthcare technologies within the MoH (Shafie, Chandriah, et al., 2019). For instance, guidelines have been developed

for managing ERTs for lysosomal storage diseases (LSDs) to maximize the benefits of limited healthcare resources (Ministry of Health Malaysia, 2012).

However, the financial burden of treating rare diseases, such as LSDs, has far-reaching societal impacts. The costs are shared among stakeholders such as patients, healthcare providers, pharmaceutical companies, and payers such as insurance companies and the government. Thus, cost reduction can have broader positive economic impacts, manifested in lower insurance premiums and a lower tax burden (Anderson et al., 2013). Moreover, implementation of newborn screening programs using modern tandem mass spectrometry, advances in genetic identification, and policy initiatives to improve and align newborn screening resources for LSDs could be a significant step towards addressing this problem. However, such an initiative does not currently exist in Malaysia, unlike countries such as Korea, Taiwan, and Australia (Therrell et al., 2015).

1.4.3 Patient Care Overhead

Malaysia operates an efficient and widespread two-tier healthcare system under the Ministry of Health (MOH). The public sector led and funded by the government, provides universal healthcare, while the private sector consists of physician-owned clinics and hospitals (Abu Bakar et al., 2014). The country has already achieved universal healthcare (UHC) through a public health system that provides broad-based health services by optimising the use of the clinical care worker workforce in the country. The public and private sectors rely on well-trained clinical care workers (HCP) to deliver high-quality healthcare. Any short-term plans to improve the system will have long-term implications for MoH expenditure if implemented on a large scale.

Patient care is time-consuming (Attard et al., 2019; Iosa et al., 2019) and complex activity (McPherson et al., 2008; Ahmadishad et al., 2019) because of the lengthy process and skill mix (Duffield et al., 2005) that healthcare personnel (HCP) engage in while performing clinical activities, patient-related tasks, administrative works, communication, and personal tasks. Generally, these multitasking activities are categorised as direct or indirect patient care activities, depending on whether the activities are performed in front of or away from the patient (Urden et al., 1997; Kilpatrick, 2011; Abbey et al., 2012). There are significant disparities in the proportion of time HCPs spend on direct and indirect care activities that have been reported in other areas of practice (Gholizadeh et al., 2014). In addition, previous studies over the last decade have demonstrated that the workload and the interplay between direct and indirect patient-related activity significantly impact the quality-of-care delivery (Netten et al., 1998; McPherson et al., 2008; Ahmadishad et al., 2019). Therefore, estimating direct contact time alone will underestimate the time required to provide care. There is an obvious need to comprehend and disseminate information regarding their progressive role as the patient's primary point of contact in this largely unexplored area of RD.

1.5 Problem statement

The ERT treatment has been available for over a decade. However, numerous challenges with diagnosing, managing, and treating MPS-II remain. In 2009, the MoH Technical Committee issued a practical standard to guide the use of ERT in lysosomal diseases. Since then, the average treatment cost for each patient has increased, ranging from RM500,000 to RM1 million annually. Unfortunately, only

RM 8.5 - RM 10 million has been allocated annually to cater for the medical needs of 28 individuals with lysosomal storage diseases (Chuah et al., 2018). However, due to the increasing number of patients and the chronic nature of these RDs, the funding provided is inadequate. Most orphan drugs are not on the standard list of MoH formulary and are procured through special approval processes (Chuah et al., 2018). As a result, several patients are receiving insufficient treatment doses and many new patients are still awaiting treatment. Moreover, ERT funding is unavailable in university hospitals and patients must seek further management and treatment funding at the Kuala Lumpur Hospital.

There is a significant burden of illness associated with MPS-II and its larger impact on health systems, families and society (García-Pérez et al., 2021). However, ERT has demonstrated long-term survival outcomes in local practices. This information is vital for healthcare policymakers to assess the value of public funding and reimbursement for orphan drugs. Thus, comparative data on incremental costs and patient health-related quality of life (HRQoL) of the treatment compared to palliative care alone need to be measured appropriately. The clinical trials generally reported treatment outcomes up to 2-5 years (Sampayo-Cordero et al., 2019). MPS-II is a progressive disease that requires life-long management where a more prolonged study duration of 10-15 years is necessary to reflect a natural clinical setting. Recent evidence has documented a 10-year and 15-year follow-up (Muenzer et al., 2017) and survival data (Burton et al., 2017) associated with the ERTI.

Alongside demonstrating the effectiveness of ERTI, the latest pharmacoeconomic guidelines require that CEA studies to include HRQoL measured as the single index utility derived from preference-based instruments such as EQ-5D-5L (Ministry of Health Malaysia, 2019). Currently, there is a lack of studies

demonstrating its value for money from the perspective of society using a robust economic model incorporating long-term effectiveness, local costs situation, and population-specific utility values. Therefore, the application of the incremental cost-effectiveness ratio (ICER) as a standard summary measure for the economic evaluation (EE) of ERTI is imperative to explore whether the high cost of lifelong treatment can be justified given the moderate clinical benefits in determining cost-effective strategies (Paulden, 2020).

Schlander et al. (2016) highlighted the discrepancy between the reimbursement of costs for orphan drug and conventional cost-effectiveness threshold (CET), i.e., RM37,000 per QALY gained adopted by MaHTAS. This discrepancy represents a key challenge in evaluating ODs where costs are often substantially higher than cost-effectiveness threshold typically applied to standard treatments. However, decision-makers still require robust evidence of cost-effectiveness to justify funding. In an effort to address the problems, some authorities are now considering value-based pricing, in which CET, or willingness to pay is correlated with the severity of the disease (Iskrov et al., 2016).

Several key controversies remain surrounding the economic evaluation of rare disease therapies (Riga et al., 2018). The applicability of standard CEA frameworks and assessing pharmaceuticals through the QALY framework depended on the analytical method used to determine these values when populations are too small for traditional cost-effectiveness criteria. Moreover, the ability of generic preference instruments to adequately capture the impact on quality of life in complex diseases affecting paediatric populations with challenging patient behaviour and severe cognitive impairment suggests that the utility values derived from the generic instruments are limited (Carlson et al., 2020).

1.6 Research Question

The primary and secondary objectives have led to the developing of the following research questions rooted in various analytical approaches as refined with the supervisory team. The preceding chapters will address this question:

i. What is the long-term cost-effectiveness of idursulfase compared to no treatment for MPS-II in Malaysia when evaluated using a partitioned survival model approach over a lifetime horizon?

ii. How can digital analysis of published survival curves and vignettes utility elicitation techniques inform health state transitions and outcomes in the economic model, given limitations in local MPS-II natural history data?

iii. What challenges exist in conducting cost-effectiveness analyses for rare diseases in Malaysia using conventional techniques? How can a streamlined open-source approach using R programming help address these limitations through enhanced flexibility, transparency and generalization of results?

1.7 Study Objective

The main objective of the study is to compare the cost and efficacy of the long-term enzyme replacement therapy of idursulfase (ERTI) with the usual standard-of-care (SOC) in the management of non-neuronopathic Hunter syndrome (MPS-II) in a tertiary care setting in Genetic Clinic Kuala Lumpur Hospital (GCKLH). The efficacy is estimated in terms of how the treatment translated its' value into outcome, which is prolonging survival and improving health-related quality-of-life. The specific objectives of the study are:

i. To compare the costs of managing patients both in the ERTI and SOC
ii. To estimate the effect of ERTI on the HRQoL and utility weights for different health states of MPS-II
iii. To compare the long-term survival outcome between the treatments as the difference in life expectancy gain using a partitioned survival model
iv. To compare the cost-effectiveness of lifelong treatment of ERTI to SOC based on standard cost-effectiveness analysis methods using the R programming language

CHAPTER 2

LITERATURE REVIEW

2.1 Evaluation of Healthcare Services

Healthcare evaluation aims to systematically assess the value, quality and economic impact of health services, health intervention programs, and technologies against scarce resources. Common approaches include needs assessment, program evaluation, performance measurement, and economic evaluation (EE). Economic evaluations provide the necessary information for an objective assessment of the clinical benefits, harms, social implications, and cost-effectiveness through evidence synthesis and economic modelling to inform reimbursement and coverage decisions.

The main economic evaluation techniques are cost-benefit analysis, cost-effectiveness analysis (CEA), cost-utility analysis using quality-adjusted life years (CUA), and cost-minimization analysis (CMA). CUA is preferred for comparability across diseases. Other key principles for a rigorous and credible evaluation are transparency, independence, reproducibility, and stakeholder involvement. As a fundamental step in conducting an EE, defining the study perspective is essential as it can have a significant impact on the trial design (Teerawattananon et al., 2014). The term “perspective” refers to the relevant costs taken into account based on the objectives of the study(Rascati, 2014). Multiple perspectives are often taken including those of payers, providers, society, and patients (Drummond et al., 2015).

The patient perspective is crucial because patients directly experience the effects of interventions (Hoomans et al., 2014). This perspective is particularly relevant when assessing the impact of treatment quality of life impacts or analysing patient out-of-pocket costs (Rascati, 2014). Payers such as insurance companies,

government bodies, or employers also represent the critical perspective when making decisions about employee health benefits or contracts with Managed Care Organizations (Hoomans et al., 2014). The societal perspective considers overall benefit to society and is essential in countries with nationalised healthcare. However, its complexity often limits its implementation in pharmacoeconomic studies (Rascati, 2014). In pharmacoeconomic research and decisions related to drug policy or formulary management, health management or insurance perspectives from institutions/providers and payers are often taken into account (Hoomans et al., 2014; Rascati, 2014). However, the most common method, at least in the UK is to use societal valuations. In this case, the general public values the health states rather than the patients (Sculpher et al., 2020). Since its introduction, there has been a proliferation of EE in the country since its introduction, as shown by a recent systematic review (Rahim et al., 2020).

CEA incorporates health benefits using quality-adjusted life years (QALYs) as the primary outcome measure. QALYs combine length of life with health-related quality of life into a single index number. In CEA, the general public value different health states using generic preference-based measures like the EQ5D. These measures produce a weight between 0-1 for various health states, with 1 representing full health and 0 representing death. Health states below 0 are possible and indicate worse than death. QALY gains are calculated based on these weights and time spent in each health state. For example, 1 year in full health equals 1 QALY, while 2 years in a health state with a weight of 0.5 equals 1 QALY (Udeh, 2020). This outcome allows a direct comparison of health improvements across different disease areas to inform healthcare resource allocation to maximise health gains from limited budgets.

CEA has become a standardised outcomes measurement to assess value by comparing a new intervention's cost and clinical effectiveness to existing treatment options. CEA measured the treatment's estimated 'cost' and any associated overhead costs of managing the underlying condition. The main output of the CEA is the incremental cost-effectiveness ratio (ICER), which is obtained by dividing the differences in overall costs by the differences in QALYs between the compared treatments or interventions. The resulting ICER requires comparison to a pre-set threshold (λ) to indicate if the new intervention represents good value for money ('cost-effective').

Figure 2.1 shows the cost-effectiveness plane (CE-Plane). The "X" represents the baseline strategy. The "λ" represents cost-effectiveness threshold (CET) where the maximum monetary value that a healthcare system or payer is willing to pay for an additional unit of health benefit to be worth funding from the budget (David et al., 2023). The incremental difference in cost and effectiveness of the new intervention compared to baseline is plotted on the plane. The decision to adopt the new intervention is guided by which quadrant it falls. The majority of new interventions fall into the top right quadrant (Drummond et al., 2015). This means that a medicine with an ICER below the threshold value λ is likely to be approved for payment while a medicine with a ratio above the threshold is likely to be turned down.