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An Overview About Rare Diseases in Saudi Arabia and Reimbursement of Orphan Drugs

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***Abstract*--**Due to the high cost of specialty drugs and the increasing pressure on health care budget, the use of economic evaluation in reimbursement decisions has become a necessity. Although economic evaluation methods have been established internationally, doubts have been raised about their use in orphan drugs. In the absence of Health Technology Assessment (HTA) agencies in the Arab world, it is almost impossible to make conscious decisions in regard funding drugs used not only in rare conditions but in all disease areas. The use of economic evaluation is increasingly growing and comparable to regulatory bodies role especially in the context of the current national transformation program 2020 and the Saudi vision 2030. One of the vision objectives is to optimize the utilization of available resources and the efficiency of government spending, which is going to be impossible to achieve with the current practice. Challenges accompanied by reimbursement decisions are and always will be a limitation in the absence of a proper framework that addresses limitation with the use of traditional methods in assessing the value of orphan and non-orphan drugs. This paper mentions the prevalence of rare conditions in Saudi Arabia, discusses the current reimbursements methods and policies in other countries, explore challenges with the use of typical methods of economic evaluation used in different countries, and provide a potential solution to tackle some of the limitations in funding rare conditions.

Keywords: Pharmacoeconomics (PE), Health Technology Assessment (HTA), Rare diseases, Orphan drugs, Reimbursement, Saudi Arabia

1. Introduction: Landscape of Rare Disease in Saudi Arabia

In the light of the high demand for specialty drugs and the rising cost of health care services worldwide, decision-makers find it difficult to designate funds for rare and life-threatening conditions. Rare diseases are conditions that affect populations not exceeding five in 10,000 individuals [1]. There are about 5,000 to 8,000 rare diseases around the world [2]. According to the Saudi Ministry of Health (MOH) website there are between 6,000 and 8,000 types of rare diseases, 80 percent of which are due to genetic causes [3]. Seventy-five percent of these conditions affect children, and thirty percent of them die before the age of five [3]. Unfortunately, most of rare conditions are incurable and impose a huge burden on the society. This paper intended to provide an overview about rare diseases in the Kingdom of Saudi Arabia. In fact, in Saudi Arabia, there is no national registry or published population-based research that estimates the actual prevalence of rare disease. Most of the published studies were single-center estimates and discussed a specific gene of a genetic condition.

According to a published study by al-Aqeel et al, there are 150 different types of neurodegenerative diseases in Saudi Arabia among children [4]. Authors listed the most commonly seen genetic and metabolic conditions in practice such as sickle cell anemia and thalassemia and summarized treatment modalities for each one of them according to the signs and symptoms. Authors highlighted the importance of genetic testing for early detection in which it might help in providing better treatment options (if available) or at least taking proper preventative measures such as prenatal diagnosis [4]. However, treatments of rare disease are either unavailable (not developed yet), very expensive and not accessible to all patients. Another publication discussed the prevalence and characteristics of spinal muscular atrophy (SMA) in Saudi Arabia [5]. SMA is a genetic disorder that affects newborns in which it causes muscular atrophy and paralysis due to the mutation/deletion of the survival motor neuron 1 (SMN1) [5]. Despite the absence of a national-based data about the disease prevalence, the author stated that SMA disorder is common in Saudi Arabia and it could be attributed to the high rate of consanguineous marriages [5]. The condition is currently managed by multidisciplinary supportive care that aim to minimize the impact of disability, address complications and improve quality of life [6, 7]. These supportive care measures may involve respiratory, gastroenterology, and orthopedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy, and social care [6, 7]. Due to the nature of the disease and the high degree of morbidity, patients with SMA have significant medical expenditure and high utilization of health services. In 2016, the U.S. Food and Drug Administration (FDA) approved Nusinersen marketed as

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(Spinraza®) as the first medicine approved for the treatment of SMA in pediatrics and adults. Nusinersen is an antisense oligonucleotide that interacts with a transcription of existing copies of the SMN2 gene which leads to the generation of functional and full-length SMN proteins [8]. This protein is known to be absent in SMA patients as a result of SMN1 gene deletion. Spinraza® is administered intrathecally as four loading doses followed by maintenance doses every four months [8]. Like most gene therapies, the cost of Spinraza® is significantly high which limit the patient access to the treatment. Spinraza® costs US$750,000 (SAR 2,812,500) in the first year and US$375,000 (SAR1,406,205) annually for the following doses in the US as of 2019 [9].

Another retrospective study concluded that Saudi Arabia has one the highest rates of inherited metabolic disorders in the world [10]. A team of researchers from the pediatrics department at King Abdulaziz Medical Center conducted a thirteen -year retrospective review of newborns medical records between the year of 2001 and 2014 [10]. Patients with Inborn errors metabolism (IEM) were identified by disease codes and diagnostic tests done for suspicious genetic/metabolic disease activity. IEM are rare genetic inherited disorders in which the body cannot properly turn food into energy. The disorders are usually caused by defects in specific proteins (enzymes) that help metabolize parts of food [10]. Researchers classified patients according to their type of disorder, out of 110,601 children born in that period, 187 patients were diagnosed with different types of IEM, including fructose intolerance, galactosemia, maple syrup urine disease (MSUD) and phenylketonuria (PKU) and so on.

2. Reimbursement Scheme in Saudi Health Care System

Currently, the Saudi MOH is the major provider of health services in the country. 60% of the total health services in Saudi Arabia is provided by MOH hospitals and primary health centers (PHC) [11]. Governmental and semi/ governmental health sector provides free and full access to health services for Saudi citizens, their employees, and their families. The private sector represents less than 30 % of the total health services provided to the public [11]. Patients treated at private sectors are covered by insurance in which they pay part of the service cost. According to the latest report published by Colliers International Co., only 13% of Saudi citizens are medically covered by private insurance companies as of 2017 [12]. Fortunately, the Saudi health-care system is going through a major transformation phase in alignment with the Kingdom vision 2030. The private sector uptake in operating outpatient clinics, inpatient service and surgeries has increased to 36.7% and 35.5 % of the total health services provided in 2016 respectively [12]. The Saudi public-private partnership (PPP) bill program was released in July 2018 to encourage private companies to invest in health care and eventually mandate personal health insurance plans for individuals. A key driver of this transformation program is to establish cost-containment policies and to improve access to care. A recent publication showed promising feedback towards PPP approach in Saudi healthcare system, However, some experts and stakeholders have doubts that PPP might negatively impact access to care [13]. Advocates addressed many challenges that need to be considered before moving forward to privatization, including the lack of mutual contractual agreements between the public and private sectors due to the outmoded nature of MOH practice [13]. Strategic planning and regulations must take place before the implementation of PPP in healthcare to account for better access to expensive drugs to ensure equity. One of the major limitations for better management of rare conditions is the accessibility and availability of Orphan drugs. Orphan drugs are defined as those medicines used in the diagnosis, prevention or treatment of rare diseases [2]. The Kingdom of Saudi Arabia is the largest country in Arab world and the distribution of population geographically is challenging to healthcare sectors in general. For orphan drugs in specific, this geographical distribution is challenging to patients and caregivers who live in rural areas as specialized care is often provided by tertiary hospitals that are located in large cities.

Patients who live in small cities and have no medical insurance must travel to seek medical attention. Financial support is also provided to the patient's caregiver/parents to cover for travel expenses and accommodation which imposes a huge economic burden on the government. Without health insurance and the current reimbursing system in the kingdom it is severely limiting to pay for orphan drugs for all patients in which it will delay treatment and lead to disease deterioration. The availability of orphan drug and gene therapy is also a challenge to health care providers in Saudi Arabia. Bureaucracy accompanied by imported goods including pharmaceuticals might delay patient's treatment plan. The MOH recommended a few suggestions to help early detection of rare conditions and support patients to receive better health services [3]. One of them is to enact legislations to support patients and their families and delivering incentives to pharmaceutical companies to develop medicines for the treatment of rare disease [3]. Additionally, a comprehensive review was published to determine the view of insurance companies about the access to orphan drugs through conducting a cost-effectiveness analysis (CEA). Although that less than 20% of insurance companies in the US uses CEA in reimbursement decisions, payers agreed on the value of the economic evaluation to guarantee better access and coverage of orphan drugs [14]. Meanwhile, recommendations have been made by stakeholders in the field in the kingdom to establish a separate entity that conducts an economic evaluation for new technologies to estimate the real value versus their cost on a long-term [15].

A decade ago, policy-makers had a prevailing insight that orphan drugs have a limited impact on the pharmacy budget since they are targeting a small population. Several reports were published to report the cost of orphan drugs worldwide. A recent study has estimated market share of orphan drugs in European Union (EU) to increase from 3% to 5% between 2010 to 2020, with an average annual cost per patient per disease of €32,242 with a range between €1,251 and €407,631 [2]. The total cost was expected to rise from €5 million in the year after approval of the first orphan drug to €143 million in Year 10, prior to declining and steadying-off at around €110 million per year in European countries and the United Kingdom (UK) [2]. The national organization of rare disease

(NORD) reported that 9.6% of the total drug spending ($451 million) was spent on orphan drugs in the United States (US) in 2017 [16]. According to Express Scripts Holding Co., one of the leading pharmacy's benefit managers in the US, the cost of orphan drugs in their formulary reached more than $70,000 for a 30-day supply, or $840,000 annually [17]. Furthermore, of the top-selling 100 drugs in the US in 2016, the average cost per patient per year for an orphan was $140,443, compared with $27,756 for an average non-orphan [17]. Unfortunately, there are no studies or reports that estimate the cost of orphan drugs in the Middle East or in the Kingdom of Saudi Arabia. Which is going to be challenging for policy-makers and researchers to implement policies regarding funding and reimbursement of gene therapy and orphan drugs. The next section will emphasize the role of economic evaluation in the decision-making process in different countries and provide a few examples of reimbursement methods.

3. The Role of Pharmacoeconomics in the Decision-Making Process

Pharmacoeconomics (PE) is the science of evaluating, analyzing and describing the value of a pharmaceutical product and comparing it to another alternative (drug/supportive care or doing nothing). It is a sub-discipline of health economics. The treatment effect is measured in physical units (morbidity/mortality or both) and the cost is expressed in monetary units. Pharmacoeconomic analysis serves as a guide to optimal healthcare resource allocation. As more expensive drugs are being developed and licensed, Pharmacoeconomic evaluations have become imperative especially in the context of the current national transformation program 2020 and the Saudi Vision 2030. An important strategic objective for 2020 transformation plan is to maximize the optimal resource allocation utilization of available resources and ensure efficiency of government spending. The governmental spending increased from SAR159 billion in 2018 to SAR172 billion in 2019 on healthcare services [18]. MOH is expected to spend about US$71 billion over five-years ending in 2020 [18]. Major projects and initiatives were developed by the MOH in the past few years to increase efficiency and reduce costs, one of them is to establish support programs to enhance the patient access to highly specialized drugs and the best care available. However, resources are scarce especially in the context of the rapidly growing population and the rising cost of medications. To rationalize the consumption of resources and optimize the benefits of healthcare services the adoption of PE concept is necessary. Around the world, Health technology assessment (HTA) agencies apply and adopt the disciple of PE evaluation to assess the real value "effectiveness" of newly approved drugs compared to their cost, develop policies and procedures for reimbursement and establish guidelines in best practice for economic analyses. The relevance of HTA in the perspective of pharmaceutical companies is increasing compared to the regulatory bodies as a market perspective is currently influenced by the coverage of third-party payers. Recommendations of HTA agencies are widely used in countries where third-party payers are involved in reimbursement of drugs. In many countries, HTA agencies work in partnership with public payers to develop a framework for decision-making including setting economic impact thresholds and developing reimbursement policies [19]. In the US, where HTA agency is absent, the largest governmental insurer program, Medicaid has a major task for many orphan medicines reimbursement and coverage. Due to the financial burden associated with the utilization of orphan drugs some states adapted prior authorization policies that are inconsistent with laws and considered legally challenging. They required Medicaid not to deny access to any necessary medication upon the participation of the manufacturer in the drug rebate program [19]. For example, Arkansas Medicaid established prior authorization criteria for an orphan drug approved for the treatment of cystic fibrosis. To ensure access of patients in need for the drug, they accomplished a legal agreement [20]. In the UK, the National Institute for Health and Clinical Excellence (NICE) established the Highly Specialized Technologies (HST) program since 2013 in order to target conditions with the incidence of two or less per 100,000 population [19]. The framework for evaluating orphan drugs in HST program is similar to non-orphan drugs but with broader domains and criteria. Reviewers at the HST program consider the disease nature, including the economic and social impact on patients and caregivers, health benefits and budget impact. In 2016, NICE increased the threshold of cost-effectiveness related to HST program to £100,000 which is approximately $125,000/QALY gained [21]. This threshold is higher than the threshold used for non- HST by about three to five times the range which is £20,000-30,000 [21]. Although NICE has full authority to recommend or not to recommend a new technology for reimbursement to the National Health Service (NHS), public comments and experts opinions matter when it comes to decision-making. As a result, NICE updated their approach and added a QALY weighting scheme [21]. This applies mainly for HST technology that has a comparator treatment with quality-adjusted life years (QALYs) gained over a lifetime 30 or higher [21]. On the other hand, some other countries admit that the concept of cost-effectiveness should be applied to orphan drugs without considering alternative thresholds. The Swedish HTA agency denied reimbursing Imiglucerase (Cerezyme®) for Gaucher disease [22, 23]. They considered that the €1 million per QALY is too high price to pay regardless of the level of benefit, although that the Swedish HTA agency has a wide threshold range which is between €35,000 - €100,000 per QALY gained [22, 23]. In other countries such as Canada, authorities abandoned any notion from CEA while determining the value of orphan drugs. In Ontario the Public Drug Programs has developed and implemented a seven-steps approach for orphan drugs funding [24, 25]. These steps include confirmation that the disease is rare, understanding the nature of the disease and the potential value of treatment, estimating treatment effectiveness and cost, generating recommendations for funding, involvement of experts and stakeholders during evaluation, and updating information and reassessing policies [24, 25]. In conclusion, there is no fixed methodology to consider in regards to funding orphan drugs. Policy-makers should set their priorities and start considering approaches that ensure equal access to

treatment that maximize clinical benefits and creates a balance between costs and effects for the health care system. The next section will discuss challenges accompanied by the use of traditional methods regarding funding orphan drugs.

4. Challenges in Applying Pharmacoeconomics Concept in Funding Orphan Drugs

There are many challenges facing policy-makers when it comes to adopting the concept of Pharmacoeconomics in health care in general. Limitations associated with the funding and access to orphan drugs will make it even harder. For starters, there is no explicit or "universal" definition of rare and/ or ultra-rare disease. The key challenge in developing policies for reimbursement is settling a clear definition for rare conditions. The definitions presented as prevalence per 100,000 population was set to enable comparison across other conditions which is not necessarily accurate in this case. Moreover, there is a significant variation in the number of cases per 100,000 individuals around the world. A range from 5 to 76 cases per 100,000 population was set as a definition of rare diseases from different organizations [19]. In the US, the FDA uses a definition established by the Orphan Drug Act in1983 and based on a prevalence of less than 200,000 patients at that time. According to the current estimation of US population, it is approximately 61 cases per 100,000 [19]. In Japan, the disease is considered rare if the prevalence is less than 50,000 patients or less than 40 per 100,000 considering the current estimate of the population [19]. Another challenge would be the ethical context of funding expensive drugs for rare conditions. The struggle of finding balance between social values and cost-effectiveness of costly treatments not only in reimbursing orphan drugs but with new technologies in many disease areas is still controversial. The concept of fairness and equity is often addressed to support setting priorities for resource allocation based on age. This notion of preferring younger over older individuals could be argued that young people could benefit more from the treatment since they might have better or higher chances of living normal and healthy lives. This concept will create tension and possible injustice to the whole health system when resources should be utilized in more prevalent conditions such as cancer, diabetes, and cardiovascular diseases. There is no simple solution to such issue, however, the decision whether to fund or not to fund an orphan drug must consider more than the drug price. The characteristics or the disease nature should be considered since most of rare conditions are usually severe, life-threatening and most of the time cause disability. The social and economic impact of the condition must also be considered when it comes to making a decision.

The negative impact on the caregiver is also a factor that might affect policy-makers to develop a relaxed policy in terms of funding and access to orphan drugs. Another challenge is the relationship between rarity and cost-effectiveness ratio [26]. Due to the small sample size enrolled in clinical trials studying orphan drugs effect on rare conditions, the high annual cost of the treatment could be justified to cover research and development cost (R&D) of an orphan drug. However, policy-makers have some doubts about the high cost and effect of the drug on a long term. Uncertainty of true effect of the drug is a major concern, the main impact of rarity on estimating cost-effectiveness is that, keeping in mind the small sample size, it is difficult to establish the long-term benefits of the treatment especially in the absence of epidemiological data to support long-term effectiveness. Another factor that might hinder establishing the cost-effectiveness of orphan drugs is that the traditional methods of estimating the QALYs could not be suitable for rare conditions. The feasibility of assessing patient-reported outcomes in rare diseases, which are measured via patients' responses to the quality of life questionnaires, will yield in inaccurate responses in case of infants and young children [19, 26]. In such scenarios, the affected infants' caregivers including parents might be chosen as a surrogate for the measurement of quality of life of these patients, although the accuracy of responses that reflect the actual quality of life is indefinite. The next section will discuss potential solutions to overcome the shortcomings of traditional economic evaluation methods.

5. Proposed Approaches to Cost-Effectiveness Analysis of Orphan Drugs

As previously mentioned, there is no traditionally used method around the world to estimate the actual value of orphan drugs. The limitations stated earlier in the previous section have led HTA agencies and policy-makers to develop alternative methods and approaches to assess the value of orphan drugs and aid stakeholders in reimbursement decisions. One of the approaches is simply not to consider CEA as a guide in coverage and reimbursement of orphan drugs [19]. Countries such as Turkey and Belgium do not necessitate pharmacoeconomic analyses while assessing orphan drugs value [27]. Policy-makers in these countries have taken into considerations other factors to evaluate the usefulness of orphan drugs such as level of unmet need and the treatment innovative character [19, 27, 28]. Another proposed method is to adjust or use different willingness-to-pay thresholds in CEA [19]. The concept behind modifying thresholds is to allow for fairness and equality in access to care for all patients. Some experts have doubts with selecting higher thresholds in order to assess the value of orphan drugs due to the lack of explicit rationale behind the concept. In addition, they failed to measure the public preference for treatment of rare diseases compared to other conditions [19, 21]. Other prospective is the ethical implication while using different thresholds for patients with rare diseases compared to others. Another proposed variation is the use of equity-weighted QALY estimation [19, 30]. In typical QALYs measurement a patient or other respondent is asked to imagine themselves being in two different health states, and to assess the relative value of spending time in health state A versus health state B, instead, the suggested method allows for inflation of QALYs in certain cases based on the disease severity. For example, in the case of SMA or another disease that affects patients' quality of life in performing daily activities that impose a burden on caregivers and the health system. The rationale for inflating or giving extra weight to QALYs in some situations would be to reflect society's perspective of equity, or fairness. While these variations on the QALY may solve certain issues around the

valuation of orphan drugs, they raise other ethical and practical concerns [29]. It is unclear whether the valuation of health states from a person-tradeoff is more relevant than a summation of individuals preferences, even from a societal perspective in the case of rare conditions. Also, adding more weights to QALYs gained from an orphan drugs effect will boost the idea of equity while simultaneously decreases the valuation of treatments for other groups, such as those with more common diseases. As stated previously, some health economist considered other domains beyond CEA, traditional methods of valuation of QALYs and typical thresholds used for assessment. To ensure that all relevant domains are considered, a formal framework would need to be developed with the input of all relevant stakeholders, including patients with the conditions under evaluation [31]. The framework should address benefits, challenges, and disadvantages of adopting the new technology from all aspects and share the decisions with the public for transparency concerns. To ensure "accountability for reasonableness" a multi-criteria decision analysis (MCDA) may be utilized, where the values assigned to each domain and the weights used to combine them are determined through a formal process and made explicit and public [31, 32]. The main concern with MCDA is that it requires additional resources and has the risk of "channeling debate" via the scoring/weighting decisions that are taken [31, 33].

6. Conclusions and Future Directions

In conclusion, it is quite challenging to make a value judgment when it comes to reimbursement of orphan drugs due to the limitations accompanied with the use of traditional methods. As illustrated in this article, stakeholders might be able to adopt alternative approaches to tackle these challenges to reach a value-based decision for reimbursement. Many challenges need to be addressed by policy-makers before making decisions regarding facilitating access to specialized drugs. First, there is no data on rare diseases prevalence and incidence rates in the country. Second, the absence of economic and humanistic burden data associated with such diseases and the lack of national registries that support reporting and serve as a source of information to health care providers and researchers. Finally, the huge variation of cost elements and prices of supportive care regimen, as well as the accessibility of specialized drugs, are key challenges for policy-makers to make value-based judgment regarding funding and reimbursement of rare disorders. Therefore, national registries must be established to overcome the shortage of prevalence data. The current transformation scheme must have more information on rare conditions economic burden to utilize our resources efficiently and finally, the establishment of a national HTA entity is deemed essential to aid policy-makers in the decision-making process.

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Author contributions: MA conducted the literature survey and wrote the manuscript. NI had the idea of the review, revised the literature survey and contributed in writing the manuscript. All authors revised the final manuscript and approved the final version.

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