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The New Model of Prioritizing Orphan Drugs: The Case Study for Hemophilia, SMA, CF and MS

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Abstract

Background: Rare diseases, characterized by low prevalence and high complexity, pose significant challenges to health systems due to the uncertainty surrounding the best diagnostic methods and availability of effective treatments.

Objectives: This study aimed to introduce new methods for prioritizing orphan drugs, with a pilot application to hemophilia, spinal muscular atrophy (SMA), cystic fibrosis (CF), and multiple sclerosis (MS).

Methods: This quantitative research, conducted at Iran's National Institute for Health Research from 2021 to 2023, employs multi-criteria decision-making models (MCDA) to evaluate the efficacy of health care technologies for "rare and hard to cure" diseases. A preliminary model was developed based on a pilot selection of seven medications, for which comprehensive data was extracted. The clinical efficacy was assessed using quality adjusted life years (QALY) as a metric. The model design was grounded on three critical factors: The annual cost of intervention per individual, the annual number of eligible patients for intervention, and the Proportion of expenses covered by the governmental budget. Additionally, the model incorporated various constraints and a regulatory coefficient, denoted as "w," to enhance its robustness.

Results: By running the model, the coverage of selected medications through model optimization, revealing the following percentages: Alemtuzumab (30%), ocrelizumab (30%), emicizumab (6%), dornase alfa (29%), tobramycin (2%), and spinraza (0.02%). Additionally, the corresponding monetary coverage in Iranian Rials is reported as follows: Alemtuzumab (27,144,000,000 IRR), ocrelizumab (109,645,200,000 IRR), emicizumab (17,360,490,000 IRR), dornase alfa (43,350,930,000 IRR), tobramycin (1,268,505,000 IRR), and spinraza (350,000,000 IRR).

Conclusions: This model has tried to solve the shortcomings of the existing models regarding the prioritization of orphan drugs by combining different factors to improve access to essential treatments for rare diseases, although it can be generally asserted that no unique model can answer all policymakers' questions regarding budget allocation of rare diseases and orphan products.

Keywords: Orphan Drugs, Resource Allocation, Health Policy

1. Background

Although the rare diseases are individually rare, as a whole they can affect a considerable portion of the population. There is no unique definition for rare diseases. In some definitions, a rare disease is defined according to its prevalence, and in another, factors like the severity of the disease, region and population, and the access to sufficient treatments may be considered (1). Based on the orphan drug Act of 1983, a rare disease is "any disease or condition that affects fewer than 200,000 people in the United States" or about 1 in 1,500 people (2). However, the definition of rare disease based on the European Commission on Public Health is "life-

threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them," which low prevalence generally means fewer than 1 in 2,000 people (3), as a whole this definitions range from 1 in 1,000 to 1 in 200,000 in the medical literature and national health plans (4).

The most recent definition of a rare disease in China was announced on September 11, 2021, during the third multidisciplinary expert seminar on the definition of rare diseases and orphan drugs in China. According to this definition, a rare disease is one that meets at least one of the following three criteria: An incidence of less than 1 in 10,000 among newborns, a prevalence of less than 1 in 10,000, or an affected population of fewer than 140,000 people (5).

According to the global genes project, about 300 million people around the world are affected by a rare disease. In addition, the estimation of the European Organization for Rare Diseases (EURORDIS) showed that between 3.5% and 5.9% of the people worldwide are involved with one of approximately 6,000 identified rare diseases (6). Eighty percent of rare diseases have known genetic causes, 50% of rare diseases impact children, and 30% of patients with rare diseases die before the age of 5 (7). The total number of patients affected by rare diseases is large (e.g., 27 - 36 million people in the EU and 25 million in the United States), posing important challenges to health care providers, particularly in the context of escalating costs (8).

Since the prevalence of rare diseases is low, the correct diagnosis method, availability of effective treatment, or clinical guarantee to improve life expectancy or quality of life is uncertain. Consequently, they impose significant clinical and economic burdens due to the risk of unmet needs and inequality in access to treatment, which can be an important challenge for health care systems (9, 10). Beside these challenges, health systems are faced with some restrictions like limited capacity in budget, human resources, and logistic services to cope with it (11, 12). Therefore, decisions about which treatments and technologies must be covered by health benefit packages can be crucial, and the issue of how to prioritize diseases according to health-related quality of life, prices of technologies, and government budget must be considered.

Today, the approval of orphan products for rare and fatal diseases has provided new opportunities for patients. The number of orphan drug market approvals has been steadily increasing over the last three decades. These are diseases of low prevalence and high complexity that can lead to death or chronic disability, and for which there are often no treatment options (12-14). In many cases, the cost of treating rare diseases is extremely high. To achieve one year of quality of life, it often requires spending over three times GDP per capita, which exceeds the cost-effectiveness threshold set by the WHO (15).

At the end of the 20th century, patients with various rare diseases had common feelings, such as the existence of large unmet medical needs (due to the lack of therapeutic alternatives) and the common feeling of being unfairly treated compared to non-rare patients (16).

These generally serious, chronic, and progressive diseases greatly affect patients, their families, and even society. While these types of products can offer a unique chance for patients with rare diseases, they are usually very expensive. These kinds of products are highly specialized treatments for very small groups of patients. The growing number of approved orphan drugs increases their budget impact despite their low prevalence, and finding solutions to cope with the challenges of how to equitably allocate scarce healthcare resources under these circumstances is imperative (14). One of the most challenging issues faced by countries is the prioritization of healthcare services, policy-making, and service management to treat rare and incurable diseases. The aspects of policy-making, organizational structure, financial resource allocation, and service control mechanisms for these diseases have always been subjects of discussion (17).

The reimbursement of orphan products or healthcare services for rare diseases through public health insurances is increasingly presenting itself as a moral problem for health system decision-makers (14, 16). It is well known that health care budgets are limited, which is why the health technology assessment (HTA) process is used to assess the value of various medical interventions and make decisions about their coverage (12, 13). All HTA and reimbursement decisions rely on an implicit, if not explicit, evaluation of value as the initial step. Policymakers and payers worldwide are making widespread efforts to better determine the value of medicines (18).

Almost all jurisdictions consider economic evaluations, budget impact analyses, and patient-reported outcomes; but less than half accept surrogate measures. Disease severity, lack of alternatives, therapeutic value, quality of evidence, and value for money are factors used in all decision-making processes; only NICE England uses a cost-effectiveness threshold.

Budget impact is considered in all jurisdictions except Sweden (19).

In countries where distinct processes for orphan medicinal products (OMPs) are already in place, the multi-criteria decision-making models (MCDA) tool is clearly well-suited for use by clinical and economic experts, as well as patient representatives, who currently advise or aspire to advise HTA bodies. Transparency is essential for delivering clear and consistent signals to investors in pharmaceutical research, ensuring that resources are allocated to R&D pathways most likely to produce the OMPs that are highly valued by the populations health care payers and their agencies are intended to serve (18).

2. Objectives

Given the necessity of a framework for making informed decisions regarding the optimal allocation of resources for rare diseases and prioritizing related health services, and considering the shortcomings of existing models, this research was conducted with the aim of designing a prioritization model for rare disease health services and improving the current models.

3. Methods

This quantitative research, conducted at Iran's National Institute for Health Research from 2021 to 2023, employs MCDA to evaluate the efficacy of treatments for "rare and hard to cure" (R&HtC) diseases. This technique has wide applications in the public and private sectors. Multi-criteria decision-making models is classified into two general categories: (1) Multi-objective decision-making (MODM) models and (2) multi-attribute decision-making (MADM) models. The former models are used for designing issues by optimizing a set of objective functions and considering defined restrictions, while the latter models are used for selecting the best choice by prioritizing and comparing various alternatives concerning each attribute.

As the MODM model was used for resource allocation modeling based on multiple objectives, it appears that this type of modeling can be helpful for budget allocation for R&HtC diseases and orphan products. This research demonstrates how MODM was applied to design a budget allocation model for R&HtC diseases and orphan products.

This is a case study of developing a suitable budget allocation model, and three steps were considered in this process. The first stage in designing the model was forming a panel of policymakers to discuss expectations from a domestic model and the limitations of policymaking in this area. This panel held several meetings with policymakers for rare and hard-to-cure diseases, experts in health economics, healthcare management, and clinical specialists. These experts shared their views on a favorable model and the criteria that must be considered in the model.

In the second stage, based on the outputs of the panel, the expected characteristics of the domestic model were extracted, which were:

(a) Efficiency of the interventions: It was emphasized that a model based on the efficiency of interventions in improving the health of patients (and society) is an essential principle. This was particularly important, as the efficacy of interventions for certain R&HtC diseases or orphan products may be less than that of interventions for common diseases. Considering the quality of these interventions, comparing the effectiveness and cost-effectiveness of these two groups was deemed irrelevant. However, focusing on interventions for hard-to-cure diseases was generally justified despite this difference in effectiveness.

(b) Patient affordability: This is also one of the main specifications for designing the model. This critical point was included in the budget allocation model to define the required budget for the provision of services.

(c) Aspects of disease management: Another distinguishing characteristic of the model is the necessity of including all aspects of disease management, such as screening, prevention, medication, surgery, supportive measures, rehabilitation, etc.

(d) Equity: This is the next factor in resource allocation considered in the proposed model. The principal objective of this consideration is to ensure the highest level of financial support at the societal level using the available resources. This can be achieved through tiered coverage of interventions for different socio-economic groups, ensuring that disadvantaged groups receive the most effective interventions. The model considers all patient groups so that no group is deprived. Although the level of services may vary based on the characteristics of the interventions and recipient groups, the model is designed so that no patient group is completely deprived of services.

The third stage involved modeling the extracted characteristics based on the outcomes of the expert panel and different goals and objectives (such as considering efficiency, affordability, equity, and including all patient groups). Based on investigations into models for budget allocation for rare diseases and orphan products, including HTA, MCDA models, and quality adjusted life years (QALY) league tables, it

appears that the best budget allocation model can be selected through linear models.

In formulating and solving linear planning issues, the modeling process focuses on objectives such as maximizing profit or minimizing costs. However, in many real-world decision-making situations, limiting organizational objectives to a single goal is not scientifically preferable. Besides maximizing profit or minimizing costs, most organizations pursue various goals, such as retaining the workforce, maximizing market share, controlling price increases, etc.

The primary objective is to define indicators and objectives for prioritization from the policymakers' viewpoint. To design a preliminary model, a few interventions for R&HtC diseases were selected as examples, and the information for each intervention was extracted. Considering that the top priority of the model is efficacy, the clinical efficacy of each intervention was derived based on credible evidence.

Subsequently, the constrained optimization model was used as the main template. This model sets numerous constraints in budget allocation and is derived from the constraints of prioritizing interventions, translated as mathematical propositions.

4. Results

To optimize the problem, the textual description is first converted into a mathematical representation. This involves defining the objective function(s) and constraints as analytical expressions that depend on the decision variables and parameters. During the optimization process, the decision variables are altered iteratively to identify the optimal solution while keeping the parameters constant. A hypothetical model based on a multi-objective planning approach was then developed using sample interventions for four example rare diseases.

The selected interventions (prescribed medicines) were alemtuzumab for multiple sclerosis (MS) patients with RR type, ocrelizumab for MS patients with RR and PP types, emicizumab for type A hemophilia with inhibitors, dornase alfa for all groups of cystic fibrosis (CF), tobramycin for all groups of CF, and nusinersen for spinal muscular atrophy (SMA) patients. It should be noted that the effectiveness of interventions can vary depending on different indications and populations. Therefore, it is essential to include these indication-based interventions in the model. This inclusion can greatly assist in decision-making for resource allocation and indication-based pricing strategies.

The clinical efficacy evaluation was conducted using QALY to measure efficacy in the model. Since the effectiveness in the proposed model is represented by QALY gain, it can be derived from the results of studies conducted in other countries, relying on the principle of transferability of effectiveness findings in economic evaluation studies, provided that the context of the studies matches the country's conditions. The annual cost of applying an intervention depends on the number of persons eligible to receive each intervention, the cost of each intervention, and the frequency of using each intervention per patient.

Budget requirements, which are fundamental inputs, are incorporated into the model based on policymakers' recommendations. Therefore, the main variables of the model were considered as outlined below (Table 1).

Besides the main variables, we also need to define constraints. To achieve this, national-level legislation (such as the constitution's text, the five-year development plan, budget-planning legislation, etc.) was reviewed, and relevant items were extracted and analyzed. It is important to regularly review these legislations to ensure they remain up-to-date and are effectively enforced. Subsequently, the most important legislations with high obligations were translated into mathematical propositions and incorporated into the model as constraints (Table 2).

In this model, it was assumed that the available budget for rare diseases was approximately 200 billion Rials. Additionally, in Iran, all services are covered by insurance up to 70%, requiring coverage for the remaining 30%. Population size for each disease was obtained from their respective disease associations.

Using mathematical algorithms, the model was run, offering a combination of interventions that can yield the highest level of effectiveness (Box 1). In addition to the mentioned inputs, a "w" coefficient was defined for each intervention, serving as a model-regulating factor. This coefficient can account for the prioritization of preventive measures over therapeutic interventions, reflect political pressures for prioritizing certain sections of a particular intervention, or serve as a measure of the efficacy quality of an intervention. It can also incorporate the social impacts of rare diseases. This coefficient must be determined in a panel involving all stakeholders, including patients and their families, the clinical team, policymakers, and disease associations.

For this part, a scoring approach was used for the suggested criteria outlined in our previous manuscript, which included health outcomes, economic criteria, disease and target population characteristics, criteria related to alternatives, evidence attributes, and other

Table 1. The Main Variables of Models

Variables	Models
X_1	Alemtuzumab cost coverage in MS (RR)
X_2	Ocrelizumab cost coverage in MS (RR)
X_3	Ocrelizumab cost coverage in MS (PP)
X_4	Emicizumab cost coverage in Hemophilia A with inhibitor
X_5	Dornase alfa cost coverage in CF
X_6	Tobramycin cost coverage in CF
X_7	Nusinersen cost coverage in SMA

Abbreviations: MS, multiple sclerosis; CF, cystic fibrosis; SMA, spinal muscular atrophy.

Table 2. The Main Constraints

No.	Constraint
1	L = health expenses per person = 10000000 (IR Rials)
2	$X_3 \geq L_3 > 0, X_1 + X_2 \geq L_{12} > 0, X_5 + X_6 \geq L_{56} > 0, X_7 \geq L_7 > 0, X_4 \geq L_4 > 0$
3	$X_j \geq 0.3(p_{jt} \times q_{jt}) \times \alpha_j$, α_j = population size for X disease, $p_{jt} \times q_{jt}$ = total cost of the intervention for one year, $X_1 \leq 0.3\,(7{,}540{,}000) \times 12{,}000$, $X_2 \leq 0.3\,(3{,}0457{,}000) \times 12{,}000$, $X_3 \leq 0.3\,(3{,}0457{,}000) \times 1{,}900$, $X_4 \leq 0.3\,(440{,}400{,}000) \times 1{,}600$, $X_5 \leq 0.3\,(28{,}689{,}000) \times 150$, $X_6 \leq 0.3(20{,}075{,}000) \times 150$, $X_7 \leq 0.3\,(6{,}000{,}000{,}000) \times 350$
4	$X_1 + X_2 + X_3 + X_4 + X_5 + X_6 + X_7 \leq 200{,}000{,}000{,}000$
5	$X_1 + X_2 \geq L_{12}$ = per capita × population = 24,000,000,000
6	$X_3 \geq L_3 = 1{,}900{,}000{,}000$
7	$X_5 + X_6 \geq L_{56} = 300{,}000{,}000$
8	$X_4 \geq L_4 = 16{,}000{,}000{,}000$
9	$X_7 \geq L_7 = 350{,}000{,}000$
10	$X_5 \geq (0.3 \times (28{,}689{,}000) \times 150) - (150{,}000 \times 150)$
11	$X_6 \geq (0.3 \times (20{,}075{,}000) \times 150) - (150{,}000 \times 150)$
12	$X_1 \geq (0.3 \times (7{,}540{,}000) \times 1{,}2000) - (200{,}000 \times 12{,}000)$
13	$X_2 \geq (0.3 \times (30{,}457{,}000) \times 12{,}000) - (200{,}000 \times 12{,}000)$
14	$X_3 \geq (0.3 \times (30{,}457{,}000) \times 1{,}900) - (200{,}000 \times 1{,}900)$
15	$X_7 \geq (0.3 \times (6{,}000{,}000{,}000) \times 350) - (6{,}000{,}000 \times (350))$
16	$X_1, \ldots, X_7 \geq 0$

factors such as equity and political considerations (12). Based on the scoring approach, each criterion was assigned a numerical score ranging from 1 to 3, where 1 represented the lowest level of attribution. The overall scores achieved for each intervention, including the contribution of individual criteria scores, were collected from each group of stakeholders. The mean score for each intervention was then calculated and used as the weight for each specific intervention.

After running the hypothetical model under the assumption of equal weight for each intervention (w = 1), the coverage of selected medications through model optimization revealed the following percentages: Alemtuzumab (30%), ocrelizumab (30%), emicizumab (6%), dornase alfa (29%), tobramycin (2%), and spinraza (0.02%). Additionally, the corresponding monetary coverage in Iranian Rials is reported as follows: Alemtuzumab (27,144,000,000 IRR), ocrelizumab (109,645,200,000 IRR), emicizumab (17,360,490,000 IRR), dornase alfa (43,350,930,000 IRR), tobramycin (1,268,505,000 IRR), and spinraza (350,000,000 IRR) (Table 3).

It is crucial to note that the values used in this model are provided as mere examples, and modifying any of the constraints, such as the budget constraint, can lead to significantly different outcomes.

5. Discussion

Box 1. The Main Objective Functions

Variables
Target dependent: Improvement of the quality of life by the activities.
$f(X_j)$ = improvement of quality of life due to the activity; X_j, J = 1,2,3…
$\text{Max} \sum_j^7 w_j \ f\left(x_j\right)$
$\text{Max} = (\gamma_1 X_1 + \gamma_2 X_2 + \gamma_3 X_3 + \gamma_4 X_4 + \gamma_5 X_5 + \gamma_6 X_6 + \gamma_7 X_7)$; W = the coefficient includes stakeholders' preferences that could not be included as obligations in the model
$\text{Max} = w_1(0.525)(12{,}000)X_1 + w_2(0.3413)(12{,}000)X_2 + w_3(0.1665)(1{,}900)X_3 + w_4(0.66)(1{,}600)X_4 + w_5(0.458)(150)X_5 + w_6(0.44)(150)X_6 + w_7(0.01)(350)X_7$

Table 3. The Results of Optimization

Rank	Disease	Subgroup	Interventions	Coverage Amount (IR Rials)	Coverage Percent
1	MS	RR	Alemtuzumab	27,144,000,000	0.3000
2	MS	RR	Ocrelizumab	109,645,200,000	0.3000
3	MS	PP	Ocrelizumab	17,360,490,000	0.3000
4	Hemophilia	A with inhib	Emicizumab	43,350,930,000	0.0615
5	CF	All	Dornase alfa	1,268,505,000	0.2948
6	CF	All	Tobramycin	88,075,000	0.0292
7	SMA	I	Spinraza	350,000,000	0.0002

Abbreviations: MS, multiple sclerosis; CF, cystic fibrosis; SMA, spinal muscular atrophy.

In an era marked by the growth of orphan drugs and a heightened focus on treating rare diseases, understanding the methods for prioritizing these drugs and diseases is critical for effective policymaking in areas such as financing, legislation, and regulation. Numerous studies have explored both the methods and criteria for setting priorities in this field. Some studies, particularly from European countries, have used approaches such as MCDA and discrete choice experiments to evaluate orphan drugs. Among these, MCDA, which involves comparing cases using multiple scoring systems and direct weighting, has gained significant traction (16-18).

However, the absence of a consistent decision-making framework has led some researchers to propose models like EVIDEM (Evidence and Value: Impact on Decision-Making) or to integrate HTA with MCDA as a novel approach (19).

In the proposed model, factors such as the interventions, type of disease, subgroups of the disease (to consider resource allocation based on indications), the number of eligible people, the annual cost of each intervention per patient, effectiveness, ceiling of deductible, and a defined coefficient as the model-regulating factor were included. One component of this coefficient is the ratio of the cost of the first year of the intervention to the total cost of the intervention over the patient's lifetime. Another component relates to policymakers' priorities, addressing considerations not included in the model's explicit constraints, such as the obligation to include certain interventions in the coverage list due to social pressures.

All the above-mentioned factors were incorporated into the model by leveraging the advantages of existing models and addressing their defects, which are discussed below.

In this study, we initially attempted to implement a prioritization model based on mMCDA using the indicators extracted from our previous research (12). However, this approach proved impractical for two reasons. First, policymakers aimed to distribute government budgets among different diseases, whereas these models only provide a ranking without specifying the financial allocation for each disease. Second, assigning quantitative values to each indicator for rare diseases is challenging due to the scarcity of data, making model design difficult. Consequently, we tested various resource allocation models through trial and error and ultimately developed the model presented in this article.

The proposed budget allocation model for rare and high-cost (R&HtC) diseases offers distinct advantages over models like MCDA and the QALY league table. One of its key strengths is its ability to support tiered intervention coverage for patients with varying

indications or economic backgrounds, unlike previous models that treated interventions as binary (either included or excluded from the insurance package).

A cost-effectiveness league table typically ranks alternative healthcare treatments by their incremental cost-effectiveness ratio (ICER). However, differences in study methodologies can impact rankings and decision-making. Moreover, league tables often lack uncertainty measures and may exclude many services under budget constraints, making them less effective for allocating resources in the context of rare diseases (20).

For instance, de Andres-Nogales et al. found that in Spain, OMPs are generally funded using the same criteria as other drugs. However, the high costs and uncertain effectiveness of treatments for rare diseases often pose challenges in meeting cost-effectiveness criteria. Despite this, many OMPs still receive funding, indicating that other factors influence these decisions. The study also emphasized the need for a more transparent system for pricing and reimbursement (21).

Another advantage of the proposed model is its incorporation of multiple decision-making rules, offering policymakers a support network for budget allocation decisions. The model's use of adjustment coefficients adds flexibility for varying decision contexts. However, this flexibility can also be a limitation; excessive adjustments may reduce the model's effectiveness, which policymakers need to carefully manage. Schey et al. included input from all stakeholder groups in their model but did not account for the constraints that could affect resource allocation (22). Kolasa et al. emphasized that merely having a distinct financing mechanism is insufficient for an effective MCDA approach. Raising awareness about the need to modify pricing and reimbursement regulations is equally crucial, and expert input is essential for bridging communication between the public and decision-makers. As social values vary across regions, it is important to tailor criteria and their importance to specific countries (23).

In conclusion, as the development and utilization of orphan drugs and treatments for rare diseases continue to expand, it becomes essential to develop effective and flexible models for prioritizing these interventions. The complexities of limited data, high costs, and uncertainty in treatment efficacy demand sophisticated decision-making frameworks that can accommodate multiple factors. The proposed budget allocation model for rare and high-cost diseases offers an advantageous approach over traditional methods like MCDA and QALY league tables, particularly in terms of tiered intervention coverage and decision-making flexibility. However, no single model can address all the nuances of healthcare budget allocation, necessitating a combination of models tailored to specific contexts.

Policymakers are urged to consider both the strengths and limitations of different approaches and adapt them to local values and resource constraints. By doing so, they can make more equitable and efficient decisions that ultimately improve access to essential treatments for patients with rare diseases.

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Footnotes

Authors' Contribution: Z. G. N., F. H. L., M. M., and M. R. M.: Contributed to design, data collection and modeling; A. O.: Contributed to design data analysis, modeling and overall supervision; Z. F., H. Sh., A. A. S., and P. A.: Contributed to design, data analysis and drafting. All authors read and approved the final manuscript.

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