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Review article

Improving Estimate of Cost/Effectiveness of Drugs for Rare Diseases

Branislava Raičević, Slobodan M. Janković

University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

SUMMARY

Background/Aim. Incremental cost/effectiveness ratio (ICER) of many drugs for rare diseases is often much higher that the accepted cost/effectiveness threshold for reimbursement, primarily due to their extremely high prices, raising the question of their availability. The aim of this article was to review necessary adjustments of methods used for cost/effectiveness analysis of drugs for rare diseases.
Methods. This article is a narrative review of methods for adjusting cost/effectiveness analysis of drugs for rare diseases in order to get more realistic estimate of ICER threshold, which is essential information for decision-makers.
Results. Inputs in cost/effectiveness analysis of a drug for rare diseases should be adjusted by changing discount rates, estimating utilities in a more precise way, excluding treatment-unrelated costs, calculating local C/E threshold, and most importantly, by negotiating drug price until the C/E threshold is not surpassed. With intensified adjusted cost/effectiveness research within the area, many uncertainties will be ended, and real-life value of many of the drugs for rare diseases will be known, influencing pricing in a sustainable direction.
Conclusion. With the adjustments, the true cost/effectiveness of a drug for rare disease will be approached, enabling evidence-based and completely transparent reimbursement decisions.

Keywords: **cost/effectiveness, cost/utility, rare diseases, willingness to pay**

Corresponding author:
Slobodan M. Janković
e-mail: sjankovic@medf.kg.ac.rs

INTRODUCTION

Although there is no a single definition of rare diseases, the majority of health care systems acknowledge certain disease as "rare" if its prevalence is below certain limit (from 0.5 : 10,000 to 6.5 : 10,000 inhabitants, depending on the country) (1 - 3). Whatever definition is used, the number of rare diseases is huge – somewhere over 7,000. Since the majority of rare diseases have some genetic disorder in the background, their treatment must be targeted, i.e. it is necessary to develop new drug that will selectively repair the genetic disorder or treat selectively the consequences of that disorder (supplementing missing molecules or blocking some inappropriately increased activity at molecular level). Development of such targeted therapy requires considerable investment (capitalized costs of clinical development per approved orphan drug were estimated to be $291 million) (4), and finally a limited number of patients can use it. In order to ease this situation for drug developers, the designation "orphan drug" was introduced by major drug agencies. In the European Union, the "orphan drug" designation is given to a product that is used for a rare disease which is life-threatening, seriously debilitating or serious and chronic, and which currently has no specific treatment or the existing treatment is disproportionally less effective than a new drug (5). Orphan drugs bear significant benefits for the pharma companies in terms of accelerated review and 10-year market exclusivity after approval, guaranteed by the health authorities. Despite the benefits granted to orphan drugs, in real life, prices of some orphan drugs go upward to the level that could not be afforded by the healthcare payers any more (6). The prices of annual therapy with orphan drugs for rare diseases ranged in Belgium from €4,600 for busulfan to €376,000 for galsulfase in 2008 (7). Although there is no accepted definition of "extremely expensive drugs for rare diseases", some authors use this designation for drugs which cost annually more than upper cost/effectiveness threshold for one quality-adjusted life year (QALY) gained in the most developed country in the world: 100,000 USD (8). The situation is further aggravated by dramatic increase in the number of new orphan drugs that are obtaining marketing authorization (more than 40% of all recently approved prescription drugs in the United States have orphan designation). For all of them, the authorization holders later require reimbursement from health insurance funds.

If classic cost/effectiveness analysis of drugs for rare diseases is made, in the majority of cases the value of Incremental Cost-Effectiveness Ratio (ICER) is above the cost-effectiveness (C/E) threshold used for non-orphan drugs. It is due to extremely high prices of the orphan drugs in the first place, but also due to costs-influencing specificities of long-term treatment of rare diseases. While in the past this was solved by letting reimbursement of drugs for rare diseases even if not cost/effective (justifying such decisions by severity of rare diseases and lack of effective therapy), such approach is not sustainable any more as drug budgets could be broken by high demands imposed by numerous orphan drugs. Although some international working groups of experts made an effort to create principles of managing this situation, they are too general and theoretical, and not of much use in practice (9). There is urgent need to find the decision-making framework which would provide effective treatment for all patients with rare diseases at prices affordable by the healthcare payers, but also sufficient for pharmaceutical companies to cover their investments, make profit and continue with the development of new drugs (10). The aim of this article was to review necessary adjustments of methods used for C/E analysis of drugs for rare diseases that could be of help in meeting the abovementioned urgent need.

ADJUSTING COST/EFFECTIVENESS ANALYSIS OF DRUGS USED IN THE TREATMENT OF RARE DISEASES

The literature about adjusting C/E analysis of drugs for rare diseases was searched in MEDLINE and GOOGLE SCHOLAR databases, retrieving records from foundation of the databases to August 2023, and using various combinations of the following search terms: "cost/effectiveness", "rare diseases", "orphan drugs" and "extremely expensive". After finding relevant records, the "snowballing" literature search was performed. However, this review was by no means systematic. There are three methodological approaches that up to now seem plausible for adjusting C/E analysis and increasing probability of truly effective rare diseases' treatments being accepted for reimbursement by relevant healthcare payers: (1) improving estimate of cost/ef-

fectiveness (C/E) ratio by adjusting inputs in pharmacoeconomic analysis; (2) setting true cost/effectiveness threshold; and (3) adding other relevant criteria to cost/effectiveness. Some of these approaches are less useful than the other (e.g. adding criteria, because their relevance is subjectively judged), but they all require attention.

Improving estimate of cost/effectiveness ratio by adjusting inputs in pharmacoeconomic analysis

There are several inputs in a C/E analysis that could be adjusted when drugs for rare diseases are in question: discount rates, utilities of various health states, disease management costs unrelated to the drug investigated, and price of the drug. Changing rules for discount rates in Health Technology Assessment (HTA) analyses may improve otherwise unfavourable position of drugs for rare diseases. Using lower discount rates for costs and effects of treatments that result with substantial life prolongation is more appropriate, since current rates underestimate gains and losses that happen later in life of a person with a rare disease (11). Also, differential discounting of costs and treatment outcomes, with lower rates for outcomes, would give more realistic estimates of cost/effectiveness, as quality of life may even increase after several decades from the initiation of a treatment for a rare disease (12).

Disease-specific quality of life measurement scales should be used for rare diseases since generic instruments are less sensitive to capture all aspects of quality of life. Before the treatment, initiation patients may rate their quality of life with generic instruments higher than it actually is, because they usually adapt to their disease, so gains in quality of life with some very effective treatment are diminished (13). Another way to have more beneficial estimate of gains in quality adjusted life years (QALYs) with new but expensive drug for a rare disease is to use the Person Trade-Off (PTO) methodology for assigning utilities to health states of patients with that rare disease. Although of questionable validity (14, 15), the PTO methodology is used instead of classic Time-Trade-Off (TTO) methodology in order to include not only opinion of the patients themselves about utility of their health states but also rating of general public: a sample of general public is questioned how many persons with moderate health condition would they trade for a certain number of persons with severe health condition if they are in a situation to help one group only. By dividing the number of persons with severe health condition with the number of persons with moderate health condition, a disutility is generated for the severe health condition. Since rare diseases usually have severe health states, with PTO, their utility before initiation of new treatment is very low, increasing gains in QALYs when the treatment starts working. However, some authors consider the TTO method more appropriate, insisting on low reliability of utility values measured by the PTO (16).

When some innovative and very effective treatment of a rare disease prolongs life for decades, it could be expected that the treatment price will drop, especially after the pharmaceutical company loses its patent protection (it usually happens 6 - 7 years after market authorization), and generic copies or biosimilars with lower prices than that of the innovative drug emerge in the market. Since a patient will continue to use such treatment for many years, the costs of the treatment will significantly drop later in their life, and this should be taken into account when building a cost/effectiveness model (17, 18).

Exclusion of disease management costs that are not related for the treatment itself would also provide for fairer estimate of cost/effectiveness of drugs for rare diseases. When life is prolonged for decades by an effective drug, these costs, if high per unit, may mount disproportionally, making new drug cost-ineffective just for the reason of prolonging life extensively (19).

When these adjustment methods were tested on an economic model of cystic fibrosis treatment by Rubin et al. (11), the base case incremental cost/effectiveness ratio (ICER) was reduced by 75%. The largest ICER reduction was caused by including the assumption of reduced drug pricing after entry of generic copies of the innovative drug to the market (45%). Although this reduction seems large in relative numbers, the ICER in that the study did not fall below 122,000 US dollars, which is still above the cost/effectiveness threshold in the majority of countries. However, there is another input whose change may substantially influence the cost/effectiveness of drugs for rare diseases if applied properly: the initial price of the drug. While reference pricing of drugs (setting the price at similar level as it is in certain reference countries) is a widespread practice, anoth-

er approach, i.e. value-based pricing, is increasingly used. Some healthcare payers decide about the price using several criteria, like burden of illness, value for money, added therapeutic benefit, or else, but there is little consistency and transparency in it. Nevertheless, the value-based pricing led to significant savings in the countries where it was used (20, 21). In order to maximize the benefit of value-based pricing and connect it with the results of C/E analysis, the Institute for Clinical and Economic Review in the United States proposed setting prices to achieve a certain cost-effectiveness threshold (20). Indeed, the ICER value already covers therapeutic benefit, safety, and value for money of the analysed drug. If the price of the drug for rare disease is lowered to the point that the ICER is not any higher than the upper C/E threshold, it is definitely the value that should be paid by the health insurance if the drug manufacturer agrees with such price. It is well recognized that a pharmaceutical company that developed innovative drug has to return the invested money while the patent protection is active, which requires high drug price. However, the same can be done with a lower price, if market exclusivity extension is negotiated with the healthcare payer and if the volume of sales reaches certain limit (which is much more likely to happen with lower prices) (22).

Setting true cost/effectiveness threshold

Long ago, the World Health Organization (WHO) and the World Bank (WB) had set the universal recommendation for C/E threshold of 1 – 3 Gross Domestic Products (GDP) per capita per QALY gained against which the Incremental Cost/ Effectiveness Ratio (ICER) of new health technology (e.g., new drug) should be judged. After extensive use of such fixed C/E threshold in cost/effectiveness analyses, more harm than good was made as many cost-ineffective health technologies came to reimbursement lists, further restricting healthcare budgets and decreasing the chances of some new, truly cost/effective technologies to be reimbursed and widely accessible to those who need them (23). Nevertheless, the majority of the countries did not legally follow this WHO and WB recommendation, and even nowadays, they do not have officially established C/E threshold for deciding whether new technology is cost/effective or not. Both situations from the past (to have fixed or not to have the C/E threshold) should be replaced by calculating the healthcare system (i.e. nation) – a specific C/E threshold. The C/E threshold for each healthcare system, usually on the national level, could be determined separately by one of the three methods: the willingness to pay, the precedent and oppotunity cost method (24). Whatever the method is used, with a concrete, local C/E threshold value based on evidence, even if not officially accepted, there is firm ground to start discussion with healthcare payers about the cost/effectiveness of new therapy for a rare disease in comparison to the standard of care (Table 1).

The willingness to pay method is usually based on obtaining information from a general pub-

Table 1. *Methods of setting the cost/effectiveness threshold*

Method	Concept	Advantages	Challenges
The willingness to pay	Based on a general public sample ratings of utilities and monetary values	Direct evidence	Usually overrated
The precedent method	Sets the C/E threshold at the highest value paid in the past	Easy to obtain data	Unlikely that healthcare payers will repeat similar decisions
The opportunity cost method	Based on healthcare needs that will not be satisfied due to budget restriction imposed by decision to finance some new and expensive treatment.	Gives the overall picture of the health insurance system	Difficult to make because key information are frequently incomoplete
The Rule of Rescue	If the new treatment saves life of a patient, the C/E threshold is increased	None	Voluntaristic and not evidence-based

lic sample: firstly on how they rate change in utility between two health states, and secondly on how much money they would pay to obtain that change. Based on this data, the willingness to pay for one QALY gained is calculated. The information may be obtained in a number of ways, like using standard questionnaire, bidding game, discrete choice, payment cards, or simple open-ended questions (24, 25). A modification of willingness to pay method uses the existing data of value of statistical life (VSL) in certain population (usually calculated on the basis of expected earnings, i.e. using human capital approach) and divides it with quality-adjusted life expectancy (in years) in this population to get the value of a QALY gained (26).

The precedent method sets the C/E threshold at the highest value paid in the past by a healthcare payer for certain treatment, calculated per QALY gained. Although the precedent method seems simple, previous funding decisions with high values per QALY are frequently inconsistent and politically motivated, and it is unlikely that healthcare payers will repeat such decisions just because they happened in the past (26).

The opportunity cost method takes into account the healthcare needs that will not be satisfied due to budget restriction imposed by decision to finance some new and expensive treatment. The most robust way to implement this method is to make "league table", i.e. to list in a table all available treatments for certain disease and sort them according to cost per QALY in an ascending order (26). The last treatment on the list with the highest cost per QALY should be abandoned, and new treatments should be considered cost/effective only if their cost per QALY is lower than that of the abandoned treatment. As construction of "league tables" is difficult to do due to frequent lack of information, easier approach is to model an increase in mortality and decrease in quality of life if certain treatments will be abandoned after restriction of the budget imposed by decision to reallocate certain amount of the budget to new, innovative treatment. The allocated amount of the budget is then divided with estimate of total QALYs lost to get the C/E threshold (27). Yet, another approach to calculation of opportunity costs is using average productivity of a health service in terms of QALYs gained. The consequences of abandoning the established treatments due to resource allocation to a new one will be then easily quantified and compared to the heath gains with the new treatment (28).

The Rule of Rescue (ROR) is one of the ways used to increase the C/E threshold for rare diseases with high mortality, where the patients are faced with the risk of imminent death. According to ROR, a society would pay much more for QALY gained if the new treatment saves life of a patient, i.e. if with the treatment the patient avoids imminent death. Although formally rejecting the ROR as being an amorphous concept based on compassion and not on economy, even the most stringent Health technology assessment agency in the world, National Institute for Health and Care Excellence (NICE), is applying the ROR for ultra-orphan drugs through its highly specialised technologies (HST) programme, increasing the C/E threshold for some of these drugs almost ten times above the threshold used for all other drugs (29).

Adding other relevant criteria to cost/effectiveness

Faced with the fact that many expensive drugs for rare diseases have the ICER above the C/E threshold, and with pressure from rare diseases patients' organizations, patients and their relatives, and press, the decision makers are striving to find some structured approach that would enable transparent and fair decisions, and yet protect the available healthcare budget from being broken. For many involved in the evaluation of drugs for rare diseases, the way-out would be introduction of additional, mostly non-economic criteria, and construction of decision matrix in which the criteria are weighted, and after rating a total score is calculated. The construction of such decision matrix is otherwise called multi-criteria decision analysis (MCDA). There is extensive literature about this topic, but majority is of theoretical nature or some proposed schemes were tested on drugs for rare diseases already accepted or rejected for reimbursement. In a recent review by Lasalvia et al. (30), the studies about MCDA and drugs for rare diseases were summarized. The criteria that were repeatedly used in many of the reviewed studies are as following: severity of the disease, comparative efficacy, availability of therapeutic alternatives, rarity of the disease, safety, cost/effectiveness, budget impact, use for single indication, innovativeness and complexity

of production. However, as a recent comprehensive review of HTA decision-making across countries have shown (31), the additional criteria besides cost/effectiveness are applied without being organized in a matrix, depending on ad hoc decisions of appointed committees. Although patients and clinicians are involved in the decision-making process in the majority of countries, in one way or another, this does not add evidence to the decisions but rather permits the influence of their interests. Variable and voluntaristic application of the criteria is probably the consequence and not the cause of the problem. In fact, the criteria are problematic conceptually: some of them are already contained in the classic HTA (cost/effectiveness) analysis (severity of the disease, comparative efficacy, availability of therapeutic alternatives, safety, cost/effectiveness, unmet needs), or in budget impact analysis (rarity of the disease, budget impact), and the others are poorly defined and loosely interpreted (use for single indication, innovativeness and complexity of production). Such set of criteria is trying to mix the principles of Pharmacoeconomics with socio-political aspects of healthcare. Therefore, it is not surprising that it cannot be consistently applied. In some countries, cost/effectiveness analysis of drugs for rare diseases is even not required if projected budget impact is below certain amount, and in others, drugs for rare diseases that are not cost/effective are still considered for reimbursement by special committees, within the framework of special procedures (31). In such a situation, a compassion of the public to patients with rare diseases that have only one treatment option which is extremely expensive, even if minimally effective, is abused by some media to create "a case" and exert additional pressure to current healthcare authorities. When political parties recognise their interests in connection with such cases, they have means to meet these interests through the influence on decisions of "special committees" in charge of reimbursement of drugs for rare diseases.

DISCUSSION

True cost/effectiveness of drugs for rare diseases should be estimated only after adjustment of key inputs in a C/E analysis (discount rates, utilities of various health states, disease management costs unrelated to the drug investigated, and price of the drug) together with evidence-based determination of C/E threshold (using one of the following methods: the willingness to pay, the precedent, and opportunity cost method) (24). The main obstacles to reliance on pharmacoeconomics of orphan drugs are tendency to obtain fast extra-profit by some drug developers and informal influence they may have on various decision-makers. The patient organizations then may be used as tool of pressure on decision-makers to accept cost-ineffective drugs for rare diseases. Since in many countries some cost-ineffective drugs for rare diseases are already accepted for reimbursement, it is now not easy to remove them from the financing and to stop new arrivals that are not any worse but also not cost/effective. This may, however, be somewhat easier for countries like Scotland, where final reimbursement decisions are based on performance of the drug in real life during 2 – 3-year probationary period (32).

Decision-making based on pharmacoeconomic evidence could be implemented with the help of international scientific and professional organizations from the field of pharmacoeconomics that should promote this idea and develop detailed and concrete guidelines for decision-making process. Having such guidelines in hand, national healthcare authorities and payers will be able to set the decision-making system, and to promote it in media, explaining its rationality and fairness to the general public. Providing full transparency of the decision-making process is also very important for sustainability of such system, as there will be many attempts of those behind the cost-ineffective drugs for rare diseases to break it down (33).

There is a great need for pharmacoeconomic studies of drugs for rare diseases, including testing of different methods for adjustment of inputs and C/E threshold. Thorough search for evidence and sound methodology of such studies would produce results that after peer review and publication in international journals would help with making and/or updating guidelines for decision-making process upon reimbursement requests for drugs for rare diseases. Exploring cost/effectiveness of each new drug for rare diseases will expand knowledge and provide wider picture, giving valuable arguments to decision-makers when deciding about particular drug (34).

Besides cost/effectiveness studies, it would be of great importance to have more cost-of-illness studies about rare diseases published and available to all interested parties. As the number of treatments of rare diseases is growing, knowing the exact costs of

each of them, and especially the structure of the costs, both direct and indirect (relative participation of costs of drugs, costs of hospitalizations and visits to specialists, costs of other healthcare services, costs of materials, transportation costs, costs for adjusting home, etc.) will provide us with reliable inputs into modelling studies of future drugs for rare diseases. Founding and maintaining the registers of patients with rare diseases would be also very helpful, as true effectiveness and safety of drugs could be directly observed, and data about healthcare utilization will be available.

Considering the awareness among scientists of uncertainty, voluntarism and non-transparency of current decision-making concerning reimbursement of drugs for rare diseases, large changes could be expected in close future. There will be more articles like this one that will initiate discussions and creation of new guidelines for decision-making about rare diseases and their treatments. With intensified research within the area, many uncertainties will be ended, and the true value of many of the drugs for rare diseases will be known, influencing pricing in sustainable direction. The five-year perspective for these positive changes seems very likely.

CONCLUSION

The way to manage successfully the problem of ever-growing number of orphan drugs for rare diseases, covering patients' needs, not discouraging pharma companies from the development of future innovative drugs and not breaking the healthcare payers' budget in the same time, is to keep cost/effectiveness as the main criterion and avoid mixing it with compassion and political concerns. Only cost/effective treatments for rare diseases should be paid for, otherwise, we will lose lives in our societies through lost opportunities to treat other patients. However, it is absolutely necessary to adjust inputs in cost/effectiveness analysis of a drug for rare diseases by changing discount rates, estimating utilities in a more precise way, excluding treatment-unrelated costs, calculating local C/E threshold, and most importantly, by negotiating drug price until the C/E threshold is not surpassed. With the adjustments, the true cost/effectiveness of a drug for rare disease will be approached, enabling evidence-based and completely transparent reimbursement decisions.

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Disclosure statement

The authors report there are no competing interests to declare.

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Unapređenje procene odnosa troškova i efektivnosti lekova za retke bolesti

Branislava Raičević, Slobodan M. Janković

Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Kragujevac, Srbija

SAŽETAK

Uvod/Cilj. Inkrementalni odnos troškova i efektivnosti (engl. *incremental cost/effectiveness ratio* – ICER) mnogih lekova za retke bolesti često je značajno veći od praga isplativosti za refundaciju, pre svega zbog izuzetno visokih cena, koje smanjuju njihovu dostupnost. Cilj ovog članka bio je da se sagledaju neophodna prilagođavanja metoda koje se koriste za analizu odnosa troškova i efektivnosti lekova za retke bolesti.
Metod. Ovaj članak predstavlja narativni pregled metoda za prilagođavanje analize odnosa troškova i efektivnosti lekova za retke bolesti, napravljen sa ciljem da se dobije realnija procena praga isplativosti, koja predstavlja suštinsku informaciju za donosioce odluka.
Rezultati. Ulazne podatke u analizu odnosa troškova i efektivnosti lekova za retke bolesti treba prilagoditi promenom diskontne stope, preciznijom procenom kvaliteta života, isključivanjem troškova koji nisu povezani sa primenom lekova, izračunavanjem lokalnog praga isplativosti i, najvažnije, korekcijom cene leka sve dok se prag isplativosti ne pređe. Uz intenzivno prilagođavanje studija odnosa troškova i efektivnosti lekova koji se koriste u ovoj oblasti, mnoge neizvesnosti biće okončane, a stvarna vrednost mnogih lekova za retke bolesti biće poznata, što će dovesti do povećanja njihove prihvatljivosti za Republički fond zdravstvenog osiguranja.
Zaključak. Prilagođavanje studija odnosa troškova i efektivnosti lekova za retke bolesti omogućiće donošenje na dokazima zasnovanih i potpuno transparentnih odluka o refundaciji troškova.

Ključne reči: **troškovi i efektivnost, troškovi i korisnost, retke bolesti, spremnost na plaćanje**