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**Challenges in
medicines funding
for rare diseases:**

**Economic
Evaluation of
medicines for rare
diseases?**

Barcelona, 12th November 2018

Marta Trapero-Bertran PhD
Universitat Internacional de Catalunya (UIC)

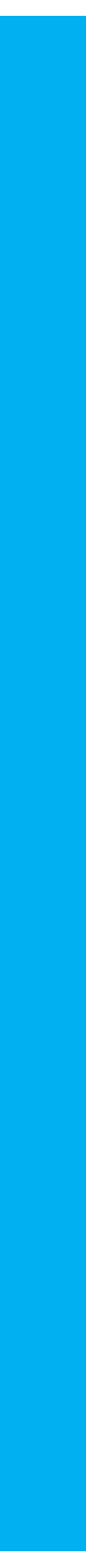
How regulators should try to pay for these drugs, in relation to the value they bring to the health system and the society?



**1. Different methods than the rest of medicines
could lead to EQUITY problems**

**2. The debate is not about the methods but value
added by these medicines**

**3. Elements of EE more sensible with rare
diseases**



NICE's continued use of
high thresholds violates
the principles of
horizontal and vertical
equity



Madrid, abril de 2016

CRITERIOS DE FINANCIACIÓN Y REEMBOLSO DE LOS MEDICAMENTOS HUÉRFANOS

Autores

Néboa Zozaya
Instituto Max Weber

Renata Villoro
Instituto Max Weber

Álvaro Hidalgo
Universidad de Castilla-La Mancha

Antonio Sarria
Instituto de Salud Carlos III

Evaluación de MMHH en Distintos Países

Tabla 4. Resumen de los criterios adicionales al coste-efectividad considerados en la práctica en los países seleccionados para la financiación/reembolso de los MMHH

	HUMANÍSTICOS				CLÍNICOS			ECONÓMICOS			OTROS
	Justicia	Equidad acceso	Regla rescate	Rareza	Severidad enf.	Alternativas	Modificación curso enf.	Coste oport.	Impacto presuprio	Sostenib. sistema	
ES		✓			✓	✓	Grado de innovación	Racionalización gasto sanitario			Utilidad social
FR					✓	✓	Valor añadido ter.		Impacto socioecon.		Tipo de tto; pos. estratég.
IT						✓			✓		Impacto sobre la inversión
DE						✓					
SW	Valor humano y solidaridad				✓				Impacto global		
BE	✓	✓	(S)		✓	✓	Valor añadido ter.		✓		Razones socioeconóm.
NL		✓				✓			✓		
UK			(S)		✓	✓	✓		✓		
AUS			✓		✓	✓			✓		
CAN		✓	✓		✓	✓					
USA			✓								

Fuentes: 33-43-45,49,50,53-55,57-64



**The debate is not about
methods but values (added
value)**



Opportunity Cost of Funding Drugs for Rare Diseases: The Cost-Effectiveness of Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Doug Coyle, PhD, Matthew C. Cheung, MD,
Gerald A. Evans, MD

Background. Both ethical and economics concerns have been raised with respect to the funding of drugs for rare diseases. This article reports both the cost-effectiveness of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and its associated opportunity costs. **Methods.** Analysis compared eculizumab plus current standard of care v. current standard of care from a publicly funded health care system perspective. A Markov model covered the major consequences of PNH and treatment. Cost-effectiveness was assessed in terms of the incremental cost per life year and per quality-adjusted life year (QALY) gained. Opportunity costs were assessed by the health gains foregone and the alternative uses for the additional resources. **Results.** Eculizumab is associated with greater life years (1.13), QALYs (2.45), and costs (CAN\$5.24 million). The incremental cost per life year and per QALY gained is CAN\$4.62 million and CAN\$2.13 million, respectively. Based on established thresholds, the

opportunity cost of funding eculizumab is 102.3 discounted QALYs per patient funded. Sensitivity and subgroup analysis confirmed the robustness of the results. If the acquisition cost of eculizumab was reduced by 98.5%, it could be considered cost-effective. **Limitations.** The nature of rare diseases means that data are often sparse for the conduct of economic evaluations. When data were limited, assumptions were made that biased results in favor of eculizumab. **Conclusions.** **This study demonstrates the feasibility of conducting economic evaluations in the context of rare diseases.** Eculizumab may provide substantive benefits to patients with PNH in terms of life expectancy and quality of life but at a high incremental cost and a substantial opportunity cost. Decision makers should fully consider the opportunity costs before making positive reimbursement decisions. **Key words:** cost utility analysis; Markov models; probabilistic sensitivity analysis. (*Med Decis Making* 2014;34:1016-1029)

REVIEW

Open Access

The quality of economic evaluations of ultra-orphan drugs in Europe – a systematic review



Y. Schuller, C. E. M. Hollak and M. Biegstraaten*

Abstract

An orphan disease is defined in the EU as a disorder affecting less than 1 in 2 000 individuals. The concept of ultra-orphan has been proposed for diseases with a prevalence of less than 1:50 000. Drugs for ultra-orphan diseases are amongst the most expensive medicines on a cost-per-patient basis. The extremely high prices have prompted initiatives to evaluate cost-effectiveness and cost-utility in EU-member states. **The objective of this review was to evaluate the quality of cost-effectiveness and cost-utility studies on ultra-orphan drugs.** We searched 2 databases and the reference lists of relevant systematic reviews. Studies reporting on full economic evaluations, or at least aiming at such evaluation, were eligible for inclusion. Quality was assessed with the use of the Consensus on Health Economic Criteria (CHEC)-list. Two-hundred-fifty-one studies were identified. Of these, 16 fitted our inclusion criteria. A study on enzyme replacement and substrate reduction therapies for lysosomal storage disorders did not perform a full economic evaluation due to the **high drug costs** and the **lack of a measurable effect on either clinical or health-related quality of life outcomes.** Likewise, a cost-effectiveness analysis of laronidase for mucopolysaccharidosis type 1 was considered unfeasible due to lack of clinical effectiveness data, while in the same study a crude model was used to estimate cost-utility of enzyme replacement therapy (ERT) for Fabry disease. Three additional studies, one on ERT for Fabry disease, one on ERT for Gaucher disease and one on eculizumab for paroxysmal nocturnal haemoglobinuria, used an approach that was too simplistic to lead to a realistic estimate of the incremental cost-effectiveness (ICER) or cost-utility ratio (ICUR). In all other studies ($N = 11$) more sophisticated pharmacoeconomic models were used to estimate cost-effectiveness and cost-utility of the specific drug, mostly ERT or drugs indicated for pulmonary arterial hypertension (PAH). Seven studies used a Markov-state-transition model. Other models used were patient-level simulation models ($N = 3$) and decision trees ($N = 1$). Only 4 studies adopted a societal perspective. All but 2 studies discounted costs and effects appropriately. Drugs for metabolic diseases appeared to be significantly less cost-effective than drugs indicated for PAH, with ICERs ranging from €43 532 (Gaucher disease) to €3 282 252 (Fabry disease). Quality of studies using a Markov-state-transition or patient-level simulation model is in general good with 14–19 points on the CHEC-list. We therefore conclude that **economic evaluations of ultra-orphan drugs are feasible if pharmacoeconomic modelling is used.** Considering the need for modelling of several disease states and the small patient groups, a **Markov-state-transition model seems to be most suitable type of model.** However, it should be realised that ultra-orphan drugs will **usually not meet the conventional criteria for cost-effectiveness.** Nevertheless, **ultra-orphan drugs are often reimbursed.** Further discussion on the use of economic evaluations and their consequences in case of ultra-orphan drugs is therefore warranted.

Keywords: Rare diseases, Orphan drugs, Cost-effectiveness, Economic evaluation, Costs and cost analysis

Social/economic costs and health-related quality of life in patients with rare diseases in Europe

Julio López-Bastida^{1,2} · Juan Oliva-Moreno^{2,3} · Renata Linertová^{2,4} · Pedro Serrano-Aguilar^{2,5}

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Although there is no single commonly accepted definition worldwide for rare diseases [1], the European Commission has agreed that rare diseases are life-threatening or chronically debilitating conditions affecting no more than 5 in 10,000 people in the European Union (EU) [2]. Despite the low frequency of each single rare disease, it is estimated that between 5000 and 8000 rare diseases have been described, affecting 6–8 % of the population in the course of their lives, for a total number of people ranging between 27 and 36 million in the EU [3–5].

While the effects of rare diseases are varied, many have serious health consequences, a high proportion being degenerative and life-threatening. About 80 % of rare diseases have a genetic origin. Approximately 50 % have a childhood onset and it is estimated that over one-third of deaths of children under the age of 1 year are due to rare diseases [6]. It is also worth noting that due to their low prevalence, the correct diagnosis of rare diseases is complex and subject to significant delays. Moreover, despite significant advances brought about by specific health

policies in recent years [2, 7], not only do most rare diseases have no cure but, for many, there is no effective treatment available or, if treatments exist, there is no guarantee of improvement in life expectancy or quality of life. The combination of these elements—severity of illness, diagnostic uncertainty, lack of effective treatments—has a strong social impact that rests largely on patients and their families.

Two insufficiently examined issues with rare diseases are (i) the economic impact caused to society, and (ii) the loss of health-related quality of life (HRQOL) for affected patients and their caregivers. Although some country-specific research on a limited set of rare diseases has been done on HRQOL and cost-of-illness [8–12], cross-national research on the socio-economic impact of rare diseases is still lacking in the EU.

The “Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe” (BURQOL-RD) project was a 3-year project under the framework of the Second Programme of Community Action in the Field of Public Health, which began in April 2010, and was promoted by the Directorate General for Health and Consumer Affairs (DG Sanco) [13]. Its objec-

Overall, the set of research articles contained in this special issue of the European Journal of Health Economics represents the broadest, most realistic research exercise providing valid information on the burden of rare diseases performed in European countries to date. **The main strength of the study lies in the use of a common methodology to assess costs and HRQOL in a wide spectrum of rare diseases in different EU countries.** The combination of the bottom-up approach to costing with the estimation of costs over a 1-year period provides a more robust and accurate picture of the medium-term burden of rare disease. These results show that, despite the relevancy of studying direct healthcare costs incurred by rare diseases, social costs are even higher, due to the loss of labour productivity and formal or informal care involved.

BURQOL-RD was made up of 12 associated partners and 8 collaborating partners, including the European alliance of patient organisations, EURORDIS (Rare Diseases Europe). The partners were from eight EU member states: Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden and the UK. Twelve participating organisations were non-profit, four were governmental, and three academic. A two-round Delphi process in combination with Carroll's diagram was used to generate consensus in the selection of the ten rare diseases among the project participants [13]. A final set of rare diseases was obtained to be targeted in the pilot study of BURQOL-RD: cystic fibrosis (CF), Prader-Willi syndrome (PWS), haemophilia, Duchenne muscular dystrophy (DMD), epidermolysis bullosa (EB), Fragile X syndrome (FXS), scleroderma, mucopolysaccharidosis (MPS), juvenile idiopathic arthritis (JIA) and histiocytosis.

Patient recruitment is a common barrier that limits the power and validity of research findings in research into rare diseases. To overcome this barrier, the BURQOL-RD research team developed a successful recruitment strategy based on online questionnaires distributed by patient organisations using e-mail [14].

The prevalence of CF was estimated in Europe at 12.6

and the mean EQ-5D VAS score was estimated to range from 51.3 to 90.

Reported figures suggest that in high-income countries belonging to the Organisation for Economic Co-operation and Development (OECD), the prevalence of haemophilia A is 14 per 100,000 males [20–23], while the yearly World Federation of Hemophilia (WFH) survey covering 106 countries, including all of Europe, estimated the prevalence of haemophilia A and B at 2.6 per 100,000 in the general population [21]. Cavazza et al. [24] showed that the lowest average annual cost per patient with haemophilia was reported in Bulgaria (€6660) and the highest in Germany (€194,490). Drugs represent nearly 90 % of direct healthcare costs in the majority of countries analysed (Hungary, Italy, Spain and Germany). In Bulgaria, France and Sweden, however, healthcare services (visits, tests and hospitalisations) prevail. The mean EQ-5D index score for adult patients was 0.69, and mean EQ-5D VAS was 66.6. The mean EQ-5D index score for caregivers was 0.87, and mean EQ-5D VAS was 75.5.

DMD is a rare disease that has a pooled prevalence of 4.8 per 100,000 males and an incidence ranging from 10.7 to 27.8 per 100,000. DMD is a rapidly progressive form of muscular dystrophy, causing increasing loss of muscle function and weakness [25–27]. Cavazza et al. [28] esti-

RESEARCH ARTICLE

Open Access

Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom



Aris Angelis^{1*}, Panos Kanavos¹, Julio López-Bastida^{2,3}, Renata Linertová^{3,4}, Elena Nicod¹, Pedro Serrano-Aguilar^{3,5} and BURQOL-RD Research Network

Abstract

Background: This study aimed to determine the societal economic burden and health-related quality of life (HRQOL) of cystic fibrosis (CF) patients in the UK.


Methods: A bottom-up cost-of-illness, cross-sectional, retrospective analysis of 74 patients was conducted aiming to estimate the economic impact of CF. Data on demographic characteristics, health resource utilisation, informal care, productivity losses and HRQOL were collected from questionnaires completed by patients or their caregivers. HRQOL was measured with the EuroQol 5-domain (EQ-5D) instrument.

Results: Using unit costs for 2012 we found that the average annual cost for a CF patient was €48,603, with direct health care costs amounting to €20,854 (42.9 % of total costs), direct non-health care costs being €21,528 (44.3 %) and indirect costs attributable to productivity losses being €6,222 (12.8 %). On average, the largest expenditures by far were accounted for by informal care (44.1 %), followed by medications (14.5 %), acute hospitalisations (13.9 %), early retirement (9.1 %) and outpatient and primary health care visits (7.9 %). Sharp differences existed depending on whether CF patients were in need of caregiver help (€76,271 versus €26,335). In adult CF patients, mean EQ-5D index scores were 0.64 (0.93 in the general population) and mean EQ-5D visual analogue scale scores were 62.23 (86.84 in the general population); among caregivers, these scores were 0.836 and 80.85, respectively.

Discussion: Our analysis highlights the importance of the economic and quality of life consequences of CF from a societal perspective. The results highlight that beyond conventional costs such as acute hospitalisations, medication and outpatient and primary care visits, indirect costs related to informal care and early retirement, have significant societal implications. Similarly, our analysis showed that the average EQ-5D index score of adult CF patients was significantly lower than in the general population, an indication that a methodological bias may exist in using the latter in economic analyses.

Conclusion: CF poses a significant cost burden on UK society, with non-health care and indirect costs representing 57 % of total average costs, and HRQOL being considerably lower than in the general population.

Keywords: Cystic fibrosis, Cost-of-illness, Social cost, Health-related quality of life, UK



Elements of EE more
sensible with rare
diseases

- 1. Price and types of cost (perspective)**
- 2. Health results (AVAC)**
- 3. Time horizon**
- 4. Sensitivity analysis**

Price and type of costs

1. Drug price
2. Bottom-up approach and estimation of costs for a continuous period
3. Importance of social costs (formal and informal care and loss of productivity) (social perspective)
4. Importance of the economic burden studies to understand the expenses that these diseases incur

Health results valuation

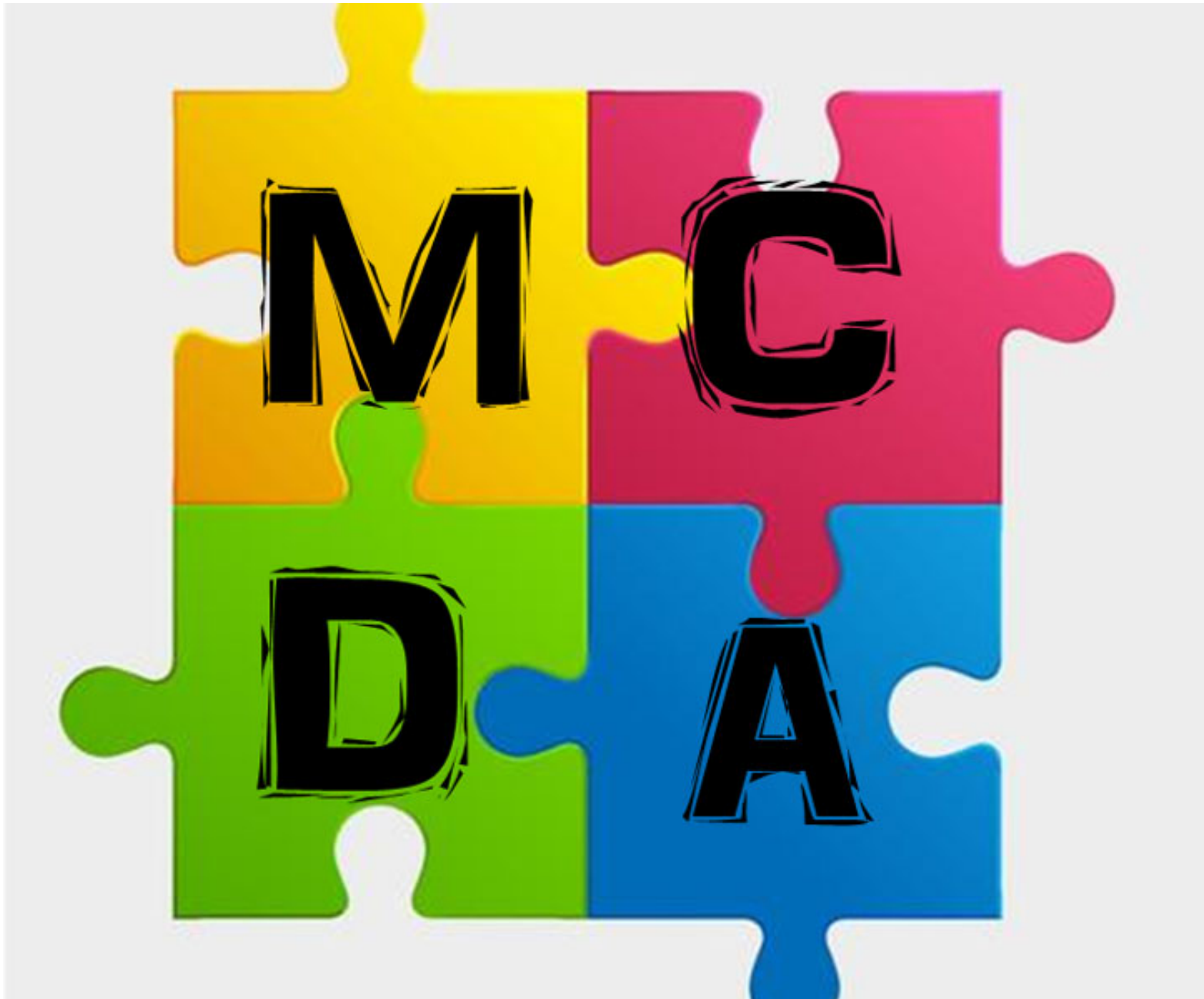
1. There is **lack of data** on the health outcome of these long-term treatments
2. It is **unknown** what is the **most appropriate unit of output** to measure the health benefit
3. Identification of the **population group most likely to benefit from this treatment** (stop treatment for non-responders and / or risk-sharing agreements)

Time horizon

- **Studies with long time horizons are missing ... (this increases the uncertainty!)**

Sensitivity analysis

- **Very important due to the magnitude of uncertainty in the analysis!**





EDITORIAL

Does MCDA Trump CEA?

Carlos Campillo-Artero¹ · Jaume Puig-Junoy^{1,2}  · Anthony J. Culyer³

7 Conclusion

MCDA's strong (procedural) points are already perfectly well adoptable (and indeed adopted) in CEA/HTA [19, 27, 28] and have been since before MCDA started to become fashionable, but the risks of double counting in MCDA; its advocates' contempt for qualitative evidence; the way they confuse expenditure, opportunity cost and harm; and its lack of ready accessibility/transparency for the public and other non-participating stakeholder all make it an **unsatisfactory vehicle for good decision making**. But we are not the ultimate judges of that—the ultimate judges are accountable decision makers. We can only adduce evidence, provide logically consistent ways of thinking about major healthcare investments and what they are intended to achieve, and suggest reasonable procedures for the appropriate involvement of stakeholders.

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Thank you very much!

mtrapero@uic.es



@marta_trapber