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Assessing the value of ODs using conventional cost-effectiveness analysis (CEA): Is it fit for purpose?

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Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose?

Maarten J. Postma[1,2], Declan Noone[3], Mark H. Rozenbaum[4], John A. Carter[5], Marc F. Botteman[5], Elisabeth Fenwick[6] and Louis P. Garrison[7*]

Abstract

Conventional cost-effectiveness analysis—i.e., assessing pharmaceuticals through a cost per quality-adjusted life year (QALY) framework—originated from a societal commitment to maximize population health given limited resources. This "extra-welfarist" approach has produced pricing and reimbursement systems that are not well- aligned with the unique considerations of orphan drugs. This framework has been slow to evolve along with our increased understanding of the impact of rare diseases, which in turn has complicated the assessment of orphan drugs meant to treat rare diseases. Herein, we (i) discuss the limitations of conventional cost-effectiveness analysis as applied to assessing access to, as well as the pricing and reimbursement of, orphan drugs, (ii) critically appraise alternative and supplemental approaches, and (iii) offer insights on plausible steps forward.

Keywords: Orphan drug policy, Pharmaceutical policy, Rare diseases, Value-based pricing, Health equity, Value of life

Background

First defined in the United States by the 1983 Orphan Drug Act, orphan drugs are products that could address an unmet clinical need but have low investment potential, primarily due to the small size of the affected population [1]. Approximately 50% of countries (Fig. 1) have enacted policies that support orphan drug research and development through strategies that include guaranteed market exclusivity, tax credits, and accelerated approval. These incentives are meant to encourage development of products to address the health needs of the 4% of the global population with a rare disease [2–5].

These orphan drug policies are controversial. On the one hand, some argue that pro-orphan drug policies address important unmet needs among persons who might otherwise experience barriers to timely and effective care and who tend to be younger and have more severe health issues [2, 5, 6]. They cite low associated per-capita spending [7] and the small share of pharmaceutical budgets attributable to orphan drugs [8] as evidence that the budgetary impact of orphan drugs is mitigated by the low prevalence of their indications. On the other hand, society bears the cost of subsidizing orphan drug development even though the acquisition costs of orphan drugs have outpaced increases in drug spending for common indications [3, 9, 10]. Further still, these policies are susceptible to manipulation, for example via "partial" orphan strategies whereby a drug is first approved for an orphan indication then for a common one but without an associated adjustment to the price [9, 11–13]. Both arguments are reasonable, but neither is complete without also considering the value that orphan drugs generate for patients with rare diseases and the broader society. Despite their mostly low overall budget impact, orphan drugs can be costly, but are they worth it?

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Orphan drugs are products that could address an unmet clinical need but have low investment potential, primarily due to the small size of the affected population.

Orphan Drug Act, US, 1983

O'Connor DJ. Orphan drug designation—Europe, the USA and Japan. Expert Opin Orphan Drugs. 2013;1:255–9.

50% of countries have enacted policies

that support OD R&D through strategies that include guaranteed market exclusivity, tax credits, and accelerated approval

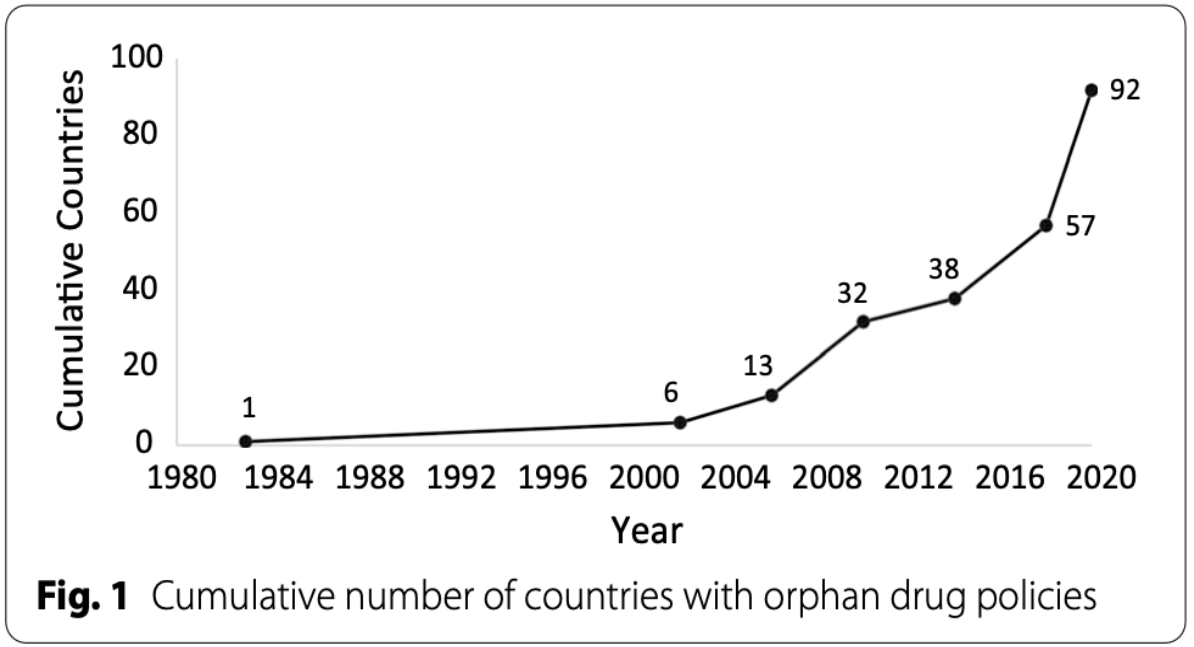

Fig. 1 Cumulative number of countries with orphan drug policies

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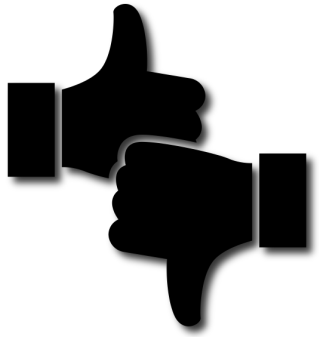
4%

Population with a **RD**

OD policies are controversial

- Some argue that pro-orphan drug policies address important unmet needs among persons who might otherwise experience barriers to timely and effective care and who tend to be younger and have more severe health issues.
- They cite
  1. Low associated per- capita spending
  2. The small share of pharmaceutical budgets attributable to ODs as evidence that the

budgetary impact of ODs is mitigated by the low prevalence of their indications



- **Society** bears the cost of subsidizing OD development even though the acquisition costs of ODs have outpaced increases in drug spending for common indications

ODs can be costly, but are they worth it?

Value

- There is **No** consensus definition of value used in health care.
- **Economically:** the “gross value” can be thought of what someone would be willing to pay for an economic good or intervention.
- The concepts of value and efficiency are related in economics.
- Broadly, achieving “economic efficiency” is obtaining maximum value for the money spent.
- Value assessments have become common place to help health systems ensure that healthcare expenditure is spent optimally.

- The process for determining economic value
- The extent of a new drug's availability
- The appropriate level of reimbursement

Cost-effectiveness analysis (CEA)

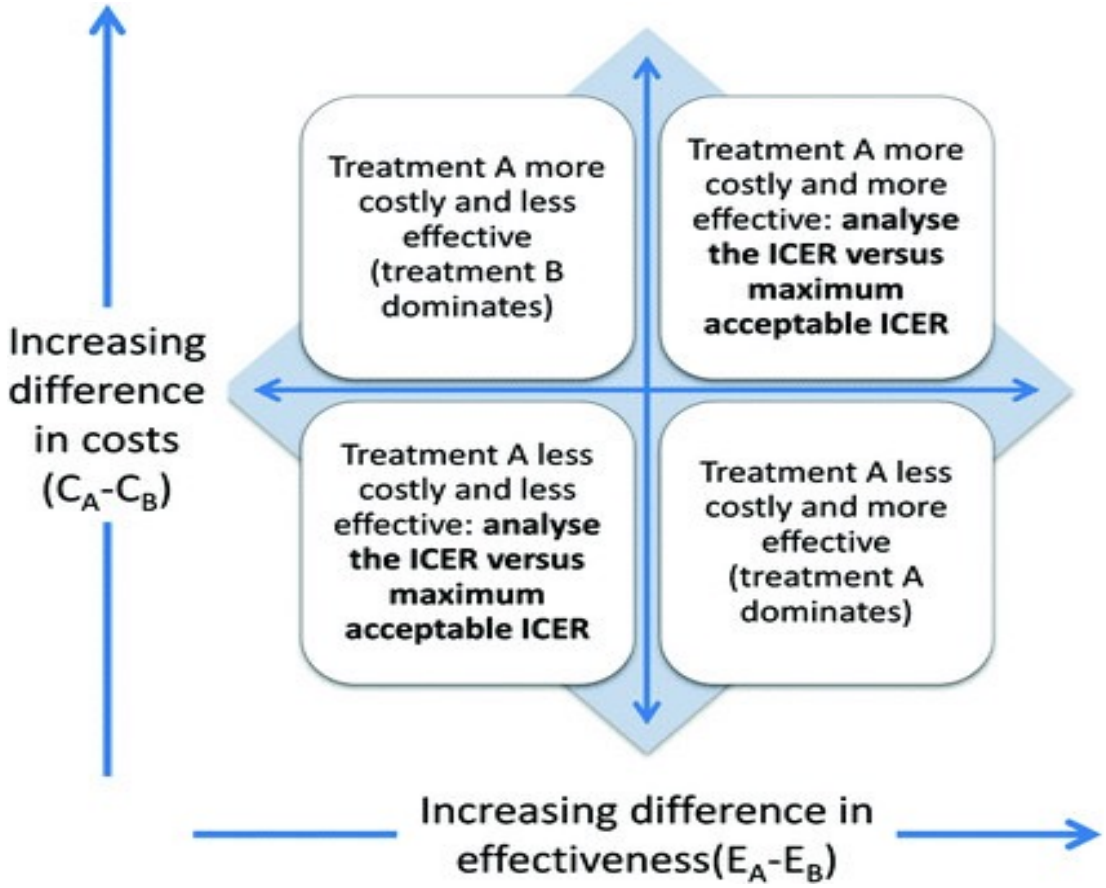
To determine if it is worth paying the additional cost associated with a new drug given the additional benefit it conveys

- **Conventional cost-effectiveness analysis (CEA):** assessing pharmaceuticals through a cost per quality-adjusted life year (QALY) framework.

- Originated from a societal commitment to maximize population health given limited resources.

Reach a decision

$$ICER = \frac{Cost(A) - Cost(B)}{Benefit(A) - Benefit(B)}$$



Evaluating ODs in this way is **inadequate** and other options are needed, ***Why?***

Conventional CEA methods have not kept pace in terms of considering the

1. Unique ways that RDs affect patient; caregivers; and society
2. How society prioritizes the needs of persons with RDs

Improving total health

Equity objectives

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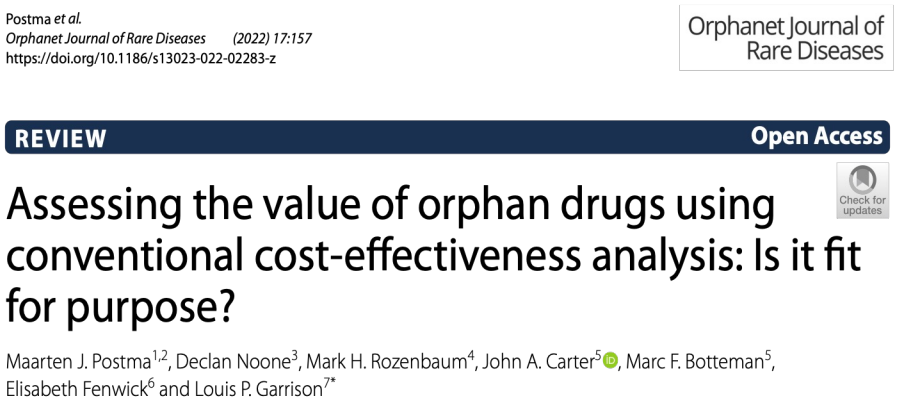
Objective



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1. Discuss the limitations of conventional cost-effectiveness analysis as applied to assessing access to, as well as the pricing and reimbursement of, orphan drugs.
2. Critically appraise alternative and supplemental approaches
3. Offer insights on plausible steps forward.

Practical and theoretical issues

1. Conflict of **basic principles**
2. The complex **nature and limited scope of the QALY** metric
3. Elevated **uncertainty**

Conflict of basic principles

1) Conflict involves **horizontal** Vs. **vertical equity**

- **Horizontal equity:** emphasizes equal treatment of equals (i.e., a ***utilitarian*** approach)— for example, applying the same cost per QALY threshold for all diseases.
- **Vertical equity:** emphasizes unequal (but equitable) treatment of the unequals and would describe a system that considers the rarity of disease in its valuation of new drugs.

- 2) Conflict involves **utilitarianism** Vs. **non – abandonment (i.e.,** maximized good for all versus favoritism toward those in dire need**)**

Conflict of basic principles

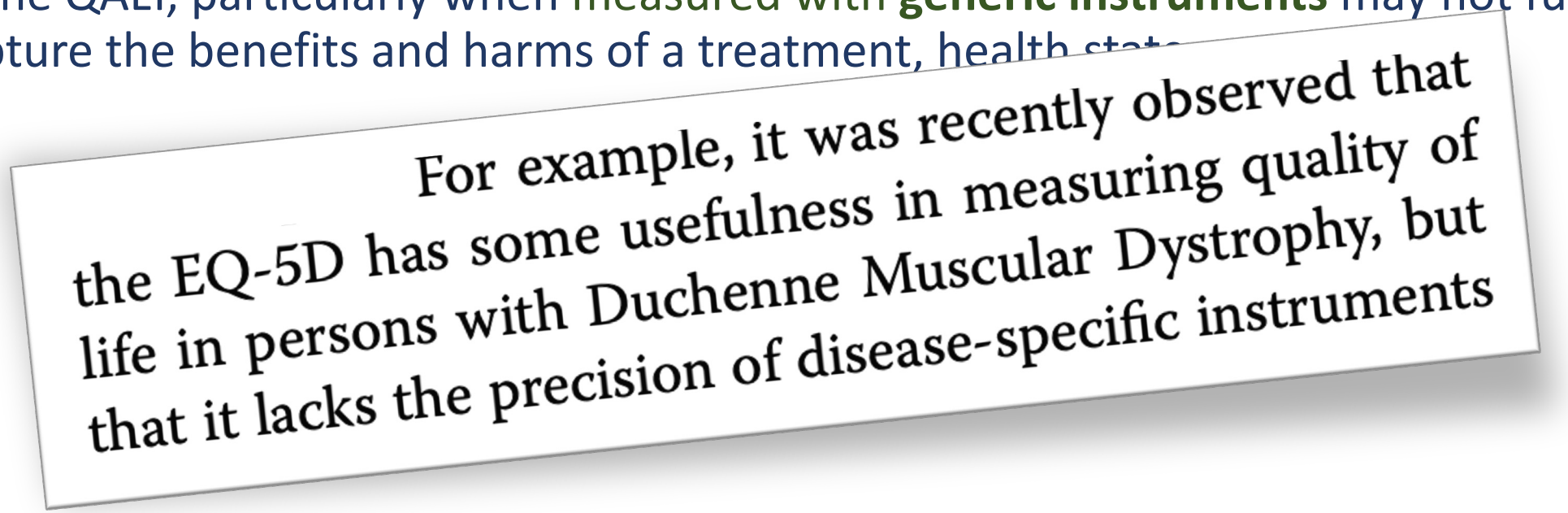
3) Conflict involves **welfarism** Vs. **extra-welfarism**

- **Welfarism:** the idea that the individual knows best what is best for their own well-being, which is broader than just health, interest. The emphasis is on individuals maximizing their well-being.

- **Extra-welfarism:** the idea that democratically-agreed principles can place limits on individual freedom in pursuit of other goals such as equity. The social welfare involves factoring in considerations of equity of access, outcomes, and well-being.

Problematic nature of the QALY

1)The QALY, particularly when measured with **generic instruments** may not fully capture the benefits and harms of a treatment, health state



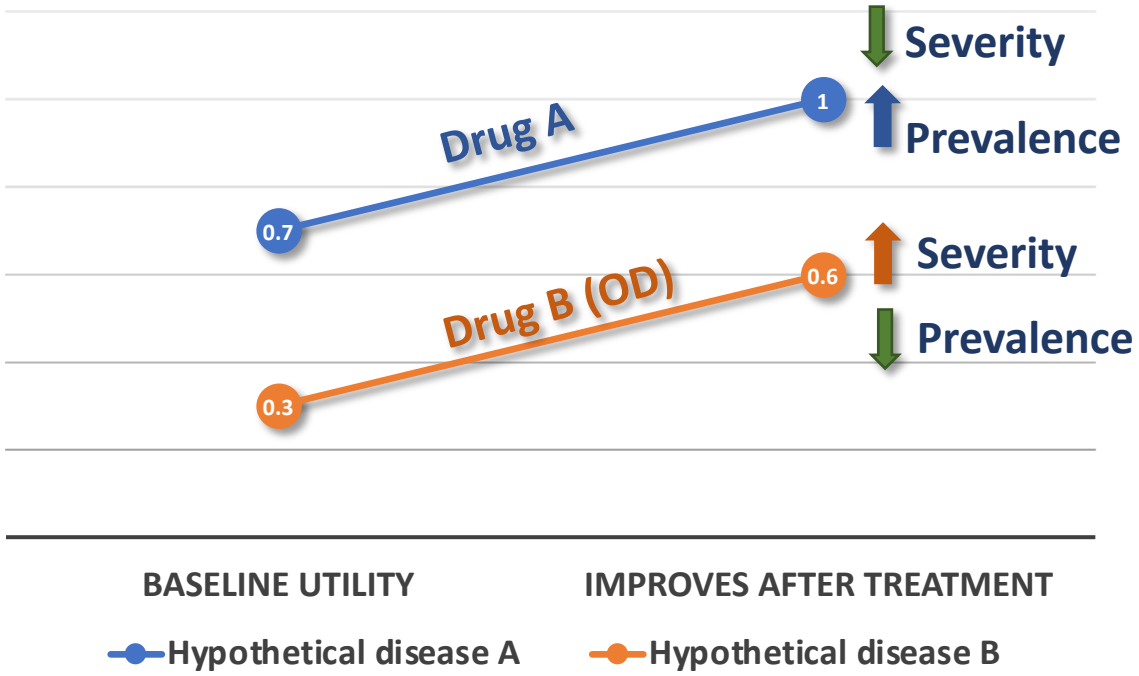
If there is a lack of differentiation among health states in terms of the associated utilities, then there will be a commensurate lack of treatment benefit.

Problematic nature of the QALY

2) **Disability paradox**: affected population judges their health more positively than does the general population.

Problematic nature of the QALY

3) conventional CEA assumes that **all QALYs are equal**, which is particularly problematic for ODs because of how severity of their given clinical indications.



Uncertainty

1) A key issue affecting the suitability of conventional CEA for ODs is uncertainty regarding **efficacy and safety** at the time the products are introduced.

- Small trial size
- Lack of randomization or comparator,
- Need to use surrogate efficacy measures,
- Uncertainty about the durability of long-term benefits

2) Some **ODs are curative** and so confer a 'value of knowing' that reduces uncertainty about the treatment response; although, it also adds a new element of uncertainty with respect to whether **the 'cure' is maintained**.

Uncertainty

3) **Financial risks to payers** caused by imprecise knowledge about the size of the rare disease population and the further impact of this on their ability to forecast future expenditures across orphan drugs and rare diseases

Alternative and supplemental approaches

- Idea of expanding the valuation context has produced several alternative approaches that consider the presence and interaction of novel concepts such as:

1. Financial and health risk protection
2. Value of hope
3. Real option value

Multicriteria Decision Analysis (MCDA)*1980s*

- Is a structured decision-making process that offers the flexibility of incorporating multiple objectives and criteria into one overall appraisal. MCDA allows various criteria to be objectively ranked or evaluated, thus generating a more definitive result than conventional discussions.

- **Limitation:** difficulties of collecting, organizing, and correctly interpreting the disparate information required to populate its comprehensive stakeholder perspective in a consistent manner that supports comparisons across diseases. Also are difficult to replicate across products and indications and particularly in the context of new patent-protected medicines.

Value Flower *Lakdawala et al, 2018*

Green circles: core elements of value
Light blue circles: common but inconsistently used elements of value
Dark blue circles: potential novel elements of value
Blue line: value element included in traditional payer or health plan perspective
Red line: value element included in societal perspective

Value Flower *Lakdawala et al, 2018*

Insurance value combine two elements:

1. **Physical risk protection** pertains to reduced fear of a disease (e.g., Alzheimer's or COVID-19) that is produced by treatments that make the "illness less unpleasant".
2. **Financial risk protection** is value created by covering the costs of treatment through a public or private insurance system.

Value Flower *Lakdawala et al, 2018*

Equity: equal access (in timing and magnitude) to healthcare, regardless of prevalence.

Limitation: Map each element into an underlying economic framwork for value assessment

Generalized risk- adjusted cost-effectiveness (GRACE)

- Conventional CEA can be biased against the more severely, or terminally, ill by not considering the impact of diminishing returns on QALY improvements.

- GRACE is approach by which quality of life returns diminish in the same way that non-health consumption gains do.

Cost-per-QALY threshold

- Researchers advocate for increasing the cost-per-QALY threshold that it is aligned with societal preferences.
- Emphasize the need to consider:

1. Rarity
2. Severity
3. Patient age
4. Unmet needs

} When deriving the ICER threshold

Conclusion

- In order to completely meet the demands of society, it is necessary to alleviate the suffering of the worst-off, hence the moral question of how to value ODs must be considered as well as technical evaluation.

- Limitation of conventional CEA toward ODs centers primarily on three points:
  1. Conflict between equity and equality
  2. Limitations of the conventional application of the QALY,
  3. How to deal with uncertainty.

- Policies for administering CEA at the national payer level have not kept pace with technological and medical advances that are yielding effective ODs.

Conclusion

- Several alternative approaches that have been developed which are primarily characterized by an emphasis on expanding the valuation framework to deal with considerations affecting value such as **uncertainty** and **equity**.

- **MCDA** and **Value Flower** are the most sensible and objective alternatives to conventional CEA.

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Thank you