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# Towards Social Cost Value Analysis:

# The Need for New Approaches for Evaluating Drugs for Ultra-Rare Diseases (URDs)


INNOVAL HC
Institute for Innovation & Valuation in Health Care

Michael Schlander, Sören Holm, Erik Nord, Jeffrey Richardson, Silvio Garattini, Peter Kolominsky-Rabas, Deborah Marshall, Ulf Persson, et al.

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## Acknowledgements

The present paper reflects the discussion that emerged during five international workshops on the evaluation of interventions for ultra-rare disorders (URDs) held in Berlin, November 08, 2012, in Dublin, November 07, 2013, in Amsterdam, November 13, 2014, in Heidelberg, September 14, 2015, and in Milan, November 12, 2015. We are indebted to the biopharmaceutical companies Alexion (during 2012), BioMarin (during 2012-2015), and Genzyme (during 2013-2015), for their support and unrestricted educational grants. The opinions expressed and any potential errors are those of the authors and should not be construed to represent the positions of the sponsors.

**Abstract**

According to the logic of cost effectiveness (analysis, CEA), health care interventions are prioritized according to their incremental cost effectiveness ratios (ICERs). Lower cost per quality-adjusted life year (QALY) gained is assumed to translate into higher social desirability of coverage. Following this paradigm, relatively low cost interventions such as sildenafil for erectile dysfunction in elderly diabetics or tattoo removals might be given higher priority for funding than many clinically effective cancer treatments and interventions for rare disorders. This apparent anomaly stimulated the authors to focus on the case of drugs for ultra-rare disorders (URDs) to explore some of the underlying issues.

Based on a comprehensive analysis of the disparate literature, the authors agreed on the need for an alternative paradigm for the economic evaluation of health care interventions. They concluded that the currently prevailing paradigm fails to capture the full social value of many interventions. Therefore, more systematic research should be devoted to the empirical measurement of social preferences and to the development of a new evaluation paradigm. Health economists should prioritize the testing and evaluation of economic methods such as social cost value analysis, rather than further rationalize and consolidate the conventional model.

## Background

From an international perspective, the National Institute for Health and Care Excellence (NICE) stands out among official Health Technology Assessment (HTA) agencies, being one of the most consistent users of cost effectiveness analysis (CEA) (Schlander 2007; Sorenson et al. 2008). The underlying logic of CEA relies on benchmarks for the maximum incremental cost per quality-adjusted life year (QALY) gained by an intervention, to be deemed an efficient use of National Health Service (NHS) resources. However, the benchmark approach has been relaxed by NICE for end of life treatments. NICE has also developed a separate process which does not rest on an assessment of cost effectiveness for the evaluation of highly specialised technologies ("HST"), considering drugs for very rare conditions (Pearce and Godfrey 2013). Yet another exemption to the use of CEA was introduced by the NHS, when it created a special Cancer Drugs Fund (CDF). The CDF was designed to enable patients to access drugs that NICE has not recommended, which may entail bypassing technology appraisals by NICE. Unsurprisingly, the resulting inconsistencies have prompted controversy (e.g., McCabe et al. 2005; Appleby 2014; Kmietowicz 2015; Mayor 2016). The CDF is now to be revised, effective from July 1, 2016, with the introduction of a "managed access" scheme combined with subsequent appraisals by NICE (Mayor 2016).

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## Anomalies of the logic of cost effectiveness

Limited resources in an NHS, or in any insurance-based health scheme, imply a need for difficult choices. Ideally, pricing and reimbursement decisions should be informed by a coherent and robust assessment and appraisal of the "value for money" of health care interventions. Assuming we can be confident that an intervention is clinically effective (the domain of evidence-based medicine), this will imply a comparative analysis of incremental costs and benefits. Adopting the current paradigm for economic evaluation of drugs and health services, reimbursement of relatively cheap interventions for moderately severe conditions might be prioritized over expensive treatments for serious or even life-threatening disorders. For example, sildenafil treatment for erectile dysfunction in elderly males or the removal of tattoos result in relatively low costs per QALY gained, because of strong individual preferences combined with relatively moderate incremental costs per patient (Stolk et al. 2000; Drummond et al. 2007). Therefore they would be given higher priority for funding than many clinically effective cancer treatments and interventions for rare disorders (Greenberg et al. 2010; Schuller et al. 2015). This apparent anomaly stimulated the authors, representing an international panel of experts in health technology assessment (HTA), health economics, evidence-based medicine, and medical ethics, to focus on the case of drugs for ultra-rare disorders (URDs) to explore some of the underlying issues.

Based on an analysis of the disparate literature related to the use of standard health economic evaluation methods for health care resource allocation (Schlander et al. 2014), the panel agreed on the need for an alternative paradigm for the economic evaluation of interventions for URDs, and of evaluation

methods more generally. Upon review of the empirical evidence, the panel concluded that the currently prevailing paradigm fails to capture the full social value of many interventions. As a consequence, priority rankings based on the logic of cost effectiveness may lead to recommendations that most people would consider highly problematic. Such rankings are based on the fundamental assumption that the social desirability of providing interventions within a collectively financed health scheme increases as their cost per QALY decreases, since this creates the opportunity for increasing the aggregate number of QALYs produced. But within a collectively financed system, the fairness of the distribution of benefits is not less important as the quantity.

Adherence to the maximization of QALYs is in striking contrast to the priorities implied in legislation designed to provide incentives for the development of treatments for rare and URDs. This legislation reflects a wide-spread political will to not disenfranchise those groups of patients from any chance of access to effective treatment. In effect, different official bodies concerned with the regulation of access to health care interventions are acting with conflicting objectives. This observation alone indicates the need to revisit the value basis of health economic evaluation principles.

## The case of ultra-rare disorders (URDs)

The high fixed cost of medical research and development in combination with relatively small target patient populations, requiring high prices per patient for pay-back of investments, virtually guarantees that the therapies that emerge from this

subsidized research will not meet the conventional criteria for cost effectiveness. The legislation favoring development and marketing of URDs reflects social values based upon health state severity and need, which contrasts with the values embodied in orthodox economic evaluation theory. Many treatments for URDs are unlikely to ever meet conventional standards for efficiency or "cost effectiveness", i.e., their incremental costs per QALY gained will frequently exceed the maximum that is commonly considered to be acceptable, such as the often-cited benchmark of £20,000 to £30,000 / QALY adopted by the National Institute for Health and Care Excellence (NICE) in England.

New drugs are generally granted an orphan designation based on a prevalence of the target disorder of fewer than 200,000 patients (in the US) or 5 per 10,000 inhabitants (in the European Union), assuming that the disease is life-threatening or chronically debilitating. NICE in England introduced an additional informal subcategory of "ultra-orphan" disorders, defined by a prevalence of less than 1 per 50,000 persons (NICE 2008). Many rare and ultra-rare disorders begin in childhood. However, rationing criteria based on cost utility analysis imply that patients unfortunate enough to be afflicted with one of those disorders are left without a fair chance to live an autonomous and fulfilling life. Following the enactment of regulation incentivizing orphan drug development, the number of orphan medicines approved by the European Medicines Agency (EMA) and by the US Food and Drug Administration (FDA) has increased steadily and now exceeds 100 (Luzzatto et al. 2015; Schuller et al. 2015). Some of these new treatments represent tremendous clinical success stories, and from there a "moral imperative" has been postulated that the health

profession should provide effective treatment if and when available (Hyry et al. 2013; Luzzatto et al. 2015).

### Opportunity costs: value foregone

Health care policy-makers and payers, however, will be concerned about the opportunity costs arising from the coverage of expensive medicines: limited resources available for health care inevitably mean that spending for URDs will be associated with a greater number of QALYs not gained by other people from, typically, larger patient populations (Phillips and Hughes 2011; Drummond and Towse 2014). Scarcity of available resources undoubtedly implies that choices need to be made. In situations of choice, economists define opportunity costs as the value of the best alternative foregone. But the process of valuation cannot eliminate or override the key moral question whether or not these choices should result in the neglect of some of the most unfortunate patients – or whether the criterion for valuation should be revised so that this outcome is avoided or mitigated.

The valuation principle for health gains underlying the QALYs approach is straightforward and based solely on length of life, weighted by individual ("selfish") preferences for the health states experienced during the respective periods of life. Health-related social value is then conceptualized as the sum total of QALYs. This is a utilitarian calculus but restricted to health outcomes narrowly defined as the length of life multiplied by health state utilities – the strengths of people's personal health state preferences. This approach ignores all other sources of value, which are relevant as people hold a broad range of non-

selfish ("social") preferences, i.e., they place value on particular social arrangements in a given context. For example, people might have a preference for living in a community that does not systematically disadvantage children with chronically debilitating or life-threatening rare disorders and only relatively expensive treatment options.

### Non-selfish ("social") preferences should matter

After more than two decades of research, there is now ample evidence that in a collectively financed health scheme the assumption that QALY maximization ought to be the primary objective is "descriptively flawed", as Paul Dolan and colleagues put it in 2005 (e.g., Dolan et al. 2005; Schlander et al. 2014). Empirical research has found that in addition to efficiency, social (i.e., "non-selfish") preferences for health care resource allocation include the severity of the condition and the urgency of an intervention – as opposed to capacity to benefit from an intervention, which is at the core of the conventional paradigm. Providing that some minimum relevant clinical benefit can be achieved, research indicates a strong preference for providing care to children and adolescents who have not yet had the opportunity to pursue their life plans autonomously and a strong dislike of "all-or-nothing" allocation decisions that would deprive whole groups of patients from any chance of effective treatment. Furthermore, some studies have found individual lifestyle choices and personal responsibility for poor health states to influence social preferences with regard to priority setting (e.g., Schlander et al. 2014).

Incorporating social preferences in decision making is not unusual in health care. For example, many countries with geographically dispersed populations provide comprehensive health care services in outlying areas, despite the associated higher costs, in order to pursue the social aim of reducing de-population due to internal migration from these areas. Since health care policy makers are agents of the population covered by a health scheme, there are compelling reasons for them to respect these social preferences.

For health economic analysis these social preferences should also matter. Recognition of social non-selfish preferences is potentially consistent with the prevailing preference consequentialist framework. Their integration into evaluation models would reconcile observed preferences with the needs of policy makers, who rely upon practical decision support. The implications, of course, are potentially far reaching: not only are not all QALYs created equal, but there are new dimensions of value to be incorporated into the valuation paradigm, in order to better approximate social value. On the costing side of the equation, adoption of a social perspective may further imply a more prominent role for budgetary impact – i.e., the transfer cost of adopting a program as opposed to the cost per individual patient as in the conventional paradigm (Richardson and McKie 2005, 2007). A focus on budgetary impact, defined by the net transfers resulting from the adoption of new program, corresponds to the social value perspective advocated here, and a small budgetary impact implies a lower opportunity cost per person when it is shared across a larger population.

There remain well-known difficulties regarding the incorporation of rights-based reasoning into a (quasi)utilitarian preference consequentialist framework. Unlike need, preferences do not translate into social claims. For example, a

preference for our favorite soccer team winning a championship does not result in any social obligation of others to support our team prevailing over a competitor. Also an approach based on social norms and preferences (sometimes referred to as "empirical ethics" (e.g., Goldenberg 2005)) has limitations, as exemplified by the existence of spiteful, discriminating, or directly inconsistent social preferences.

## Towards social cost value analysis

Notwithstanding the *caveats* above, an alternative evaluation approach built on social cost value analysis is feasible (e.g., Nord 1999; Richardson and McKie 2005, 2007) and may be developed to meet the practical needs of policy makers and health technology assessment experts. Once operationalized and adopted, it might also enable HTA agencies such as NICE to overcome the need to exempt separate categories from traditional cost effectiveness benchmarking: end of life treatments, ultra-orphan medicines and a separate earmarked budget for cancer drugs.

Hence, more systematic research should be devoted to the empirical measurement of social preferences and to the development of a new evaluation paradigm. In our view, health economists should prioritise the testing and evaluation of economic methods rather than further rationalise and consolidate the conventional model, which fails to capture relevant social norms and preferences.

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