UNIVERSITÄT
HEIDELBERG

Incremental Cost per Quality-Adjusted Life Year Gained?

The Need for Alternative Methods to Evaluate Medical Interventions for Ultra-Rare Disorders

Michael Schlander,
Silvio Garattini, Peter Kolominsky, Erik Nord, Ulf Persson, Maarten Postma, Jeffrey Richardson, Steven Simoens, Oriol de Solá-Morales, Keith Tolley, and Mondher Toumi

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INNOVAL HC
Institute for Innovation & Valuation in Health Care

& Mannheimer Institut für Public Health – www.miph.uni-hd.de

Analysis

"**Right of Access**:

An individual suffering from a rare disease has the same **right** to the necessary treatments and medication as someone with a more common disease."[1]

[1]**European Charter of Patients' Rights (Rome, 2002)**

Analysis

International Orphan Drug Legislation

- USA: Orphan Drug Act (1983); Orphan Drug Regulation (1993)
- Japan: Orphan Drug Regulation (1993)
- Australia: Orphan Drug Policy (1997)
- European Union: Regulation CE No. 141/2000 (2000)

Some Measures:

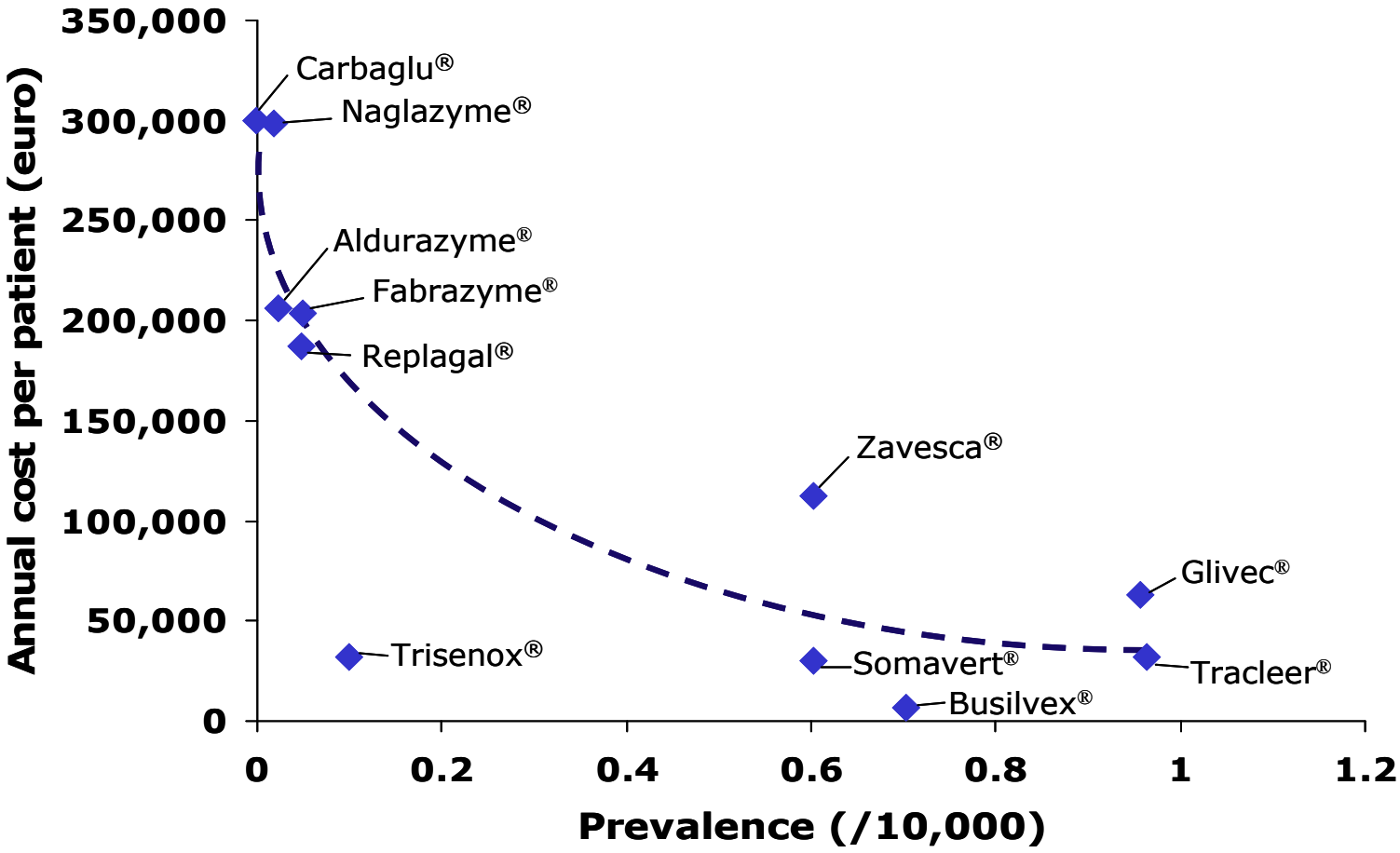
- R&D grants, tax credits, protocol assistance, accelerated review, market exclusivity (USA, 7y; Japan and EU, 10y; Australia, 5y)

Some Definitions:

- USA: prevalence < 7.5/10,000 (i.e., <200,000)
- Japan: prevalence <4/10,000
- Australia: prevalence <1.1/10,000
- European Union: prevalence <5/10,000
- England / Wales: “ultra-orphan” disorders, prevalence <1/50,000

Analysis

Prevalence and Cost per Patient



Consensus

How to Evaluate Interventions for URDs?

- **International Expert Workshop**
  - in conjunction with Annual European ISPOR Congress in Berlin / Germany, November 08, 2012
  - supported by two biopharmaceutical companies[1] under an unrestricted educational grant policy
- **Objective to Seek Agreement**
  - on challenges that arise when applying conventional HTA methodologies to ultra-rare disorders (URDs)
  - on the need for (improved or) alternative evaluation methods, ideally in the form of a Consensus Statement
  - on potential ways forward

[1]Alexion and BioMarin

Consensus

How to Evaluate Interventions for URDs?

- **Approach Chosen (Method)**
  - open exchange of views under the Chatham House Rule
  - subsequent to the workshop,
    iterative process leading to final consensus document
- **Subject of Analysis**
  - technologies targeting ultra-rare disorders (URDs), excluding cancer and personalized medicine
  - URDs under consideration should be
    - severe,
    - chronic,
    - represent clearly defined biological entities (i.e., are not created by artificial “slicing” of a biologically much broader and more prevalent indication),
    - are associated with a broadly accepted high unmet medical need

Consensus

How to Evaluate Interventions for URDs?

- **Situation Analysis**
  - The workshop participants agreed to begin with a review of the current situation and challenges.
  - The group agreed to focus on a high-level analysis (1, below):
- **Levels of Analysis**
  1. **principles underlying the current evaluation framework**
  2. actual evaluation policies implemented by HTA agencies and regulatory bodies (primarily those concerned with pricing and reimbursement decisions)
  3. evaluation practice when principles and policies are applied to real-world problems.

     In particular, the third level of analysis would have to include case studies, including cases where existing regulation has been potentially misused.

Consensus

Key Challenges for URDs

- **Establishing Evidence of Clinical Effectiveness**
  - usually very small number only of physicians with specialized expertise, who tend to be based in few specialized centers;
  - often limited clinical understanding of disorder;
  - often limited understanding of natural history of disorder;
  - often limited availability of validated instruments to diagnose and measure disease severity / progression;
  - often resulting in difficulties to generate a large volume of clinical evidence based on RCTs, which may lead to
  - higher levels of uncertainty surrounding effect size estimators;
  - small numbers of patients are often geographically dispersed, resulting in the need to establish multiple clinical trial sites for only a small number of patients;
  - …

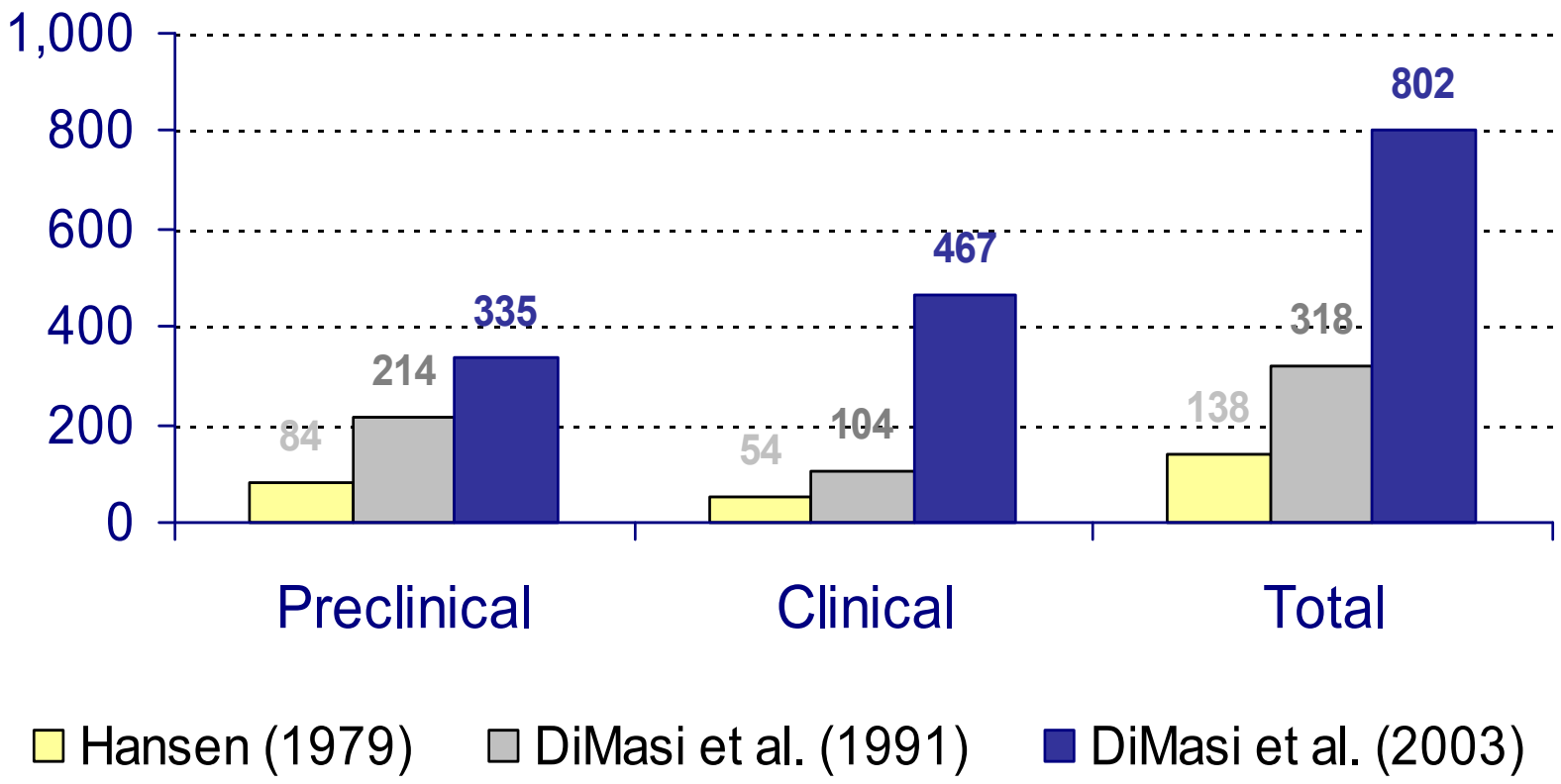
Consensus

Key Challenges for URDs

- **Establishing "Value for Money" (Efficiency)**
  - international heterogeneity in institutional arrangements and established methodologies to determine "value for money";
  - the still prevailing "logic of cost-effectiveness", relying on cost per QALY benchmarks, in applied health economics;
  - the broadly held assumption that the social desirability of an intervention would be inversely related to its associated incremental cost per QALY gained;
  - the adoption of "efficiency-first" instead of "fairness-first" evaluation approaches in a number of jurisdictions;
  - the high fixed (i.e., volume-independent) cost of R&D and the need to recoup this investment from a small number of patients during limited periods of market exclusivity;
  - …

Analysis

The Fixed Cost of Pharmaceutical R&D



Analysis

Some ICERs for URD Treatments

Condition	Prevalence	Product	ICER ("preliminary estimated £ per QALY")
M. Gaucher (Type I and III)	270	Imiglucerase (Ceredase^{R})	391,200
MPS Type 1	130	Laronidase Aldurazyme^{R})	334,900
M. Fabry	200	Agalsidase beta Fabrazyme^{R})	203,000
Hemophilia B	350	Nonacog alpha (BeneFIX^{R})	172,500
M. Gaucher (Type I)	270	Miglustat	116,800

[1]adapted from NICE (2005)

Analysis

Some Cost-Effectiveness Benchmarks

- **Some international "de facto" benchmarks:**
  - **New Zealand** (PHARMAC):
    NZ-$ 20,000 / QALY[1]
  - **Australia** (PBAC):
    AUS-$ 42,000 / LYG to AUS-$ 76,000 / LYG[2]
  - **England and Wales** (NICE):
    £ 20,000 – £ 30,000 / QALY
  - **United States** (some MCOs):
    US-$ 50,000 – US-$ 100,000 / QALY[3]
  - **Canada** (proposed "grades of recommendation"):
    CAN-$ 20,000 – CAN-$ 100,000 / QALY[4]
- **No scientific basis**

[1]C. Pritchard (2002); QALY: "quality-adjusted life year"; [2]George et al. (2001); LYG: "life year gained"
[3]D.M. Cutler, M. McClellan (2001); [4]A. Laupacis et al. (1992)

Consensus

Adopting the Logic of Cost Effectiveness

… using Incremental Cost-per-QALY-Gained Benchmarks …

… would have the potential

to necessarily and inevitably deprive many patients

with URDs from any chance to ever get access

to innovative, effective interventions.

The Underlying Premise

Analysis

"A QALY is a QALY is a QALY – regardless of who gains and who loses it."[1]

"The principal **objective** of the *National Health Service* **ought** to be **to maximize the aggregate improvement** in the health status of the whole community."[2]

"The underlying **premise** of CEA in health problems is that for any given level of resources available, **society** (or the decision-making jurisdiction involved) **wishes to maximize the total aggregate health benefit** conferred."[3]

[1]D. Feeney and G.W. Torrance (1989)

[2]Anthony J. Culyer (1997)

[3]M.C. Weinstein and W.B. Stason (1977)

Analysis

The Underlying Premise

"Social Desirability of an Intervention is Inversely Related to its Incremental Cost per QALY Gained" - but:

- Sildenafil for elderly diabetics with erectile dysfunction and removal of tattoos appear to be associated with a relatively (very) low cost per QALY gained,

  whereas

- palliative care, interventions for people with comorbid conditions (in "double jeopardy", like the disabled) or (very) rare disorders appear to be associated with (very) high cost per QALY gained.

Individual Preferences versus Social Preferences; Individual Utility versus Social Utility:

- Do individual preferences map into social utility, i.e., is social WTP simply the sum of individual WTP?
- As to WTP and ATP, what is the appropriate budget constraint?

Analysis

Three Areas of Concern

Normative Reasons for Concern

- (Quasi) Utilitarian "efficiency-first" framework, implying
- distinct difficulties to incorporate rights-based reasoning.

Empirical Reasons for Concern

- Studies overwhelmingly indicate that the majority of people do not wish QALY maximization, and suggest
- a wide range of social preferences (other than QALY maximization).

Methodological Reasons for Concern[1]

- Valuation results (for VSL / QALYs, and for health state utilities alike) differ greatly as a function of the methodology chosen.

[1]not addressed here

Analysis

What are the Objectives of Health Care?[1]

Utilitarian Thought[2]	Deontological Thought[2]
Economic Welfare Theory (ordinal utilitarianism) **Extrawelfarism** (cardinal medical utilitarianism)	**Health Care Sector** (Majority of) Professionals and the Public
	Stated (Official) Objectives Policy Makers, Payers, Providers
	Historic Roots of Medicine and Health Care
	"Empirical Ethics" (Public Preferences)
	Legal Environment (Constitutional Provisions)
Moral Intuitions (e.g., Bentham, Mill, Harsanyi)	**Moral Intuitions** (e.g., Kant; Rawls, Daniels; Sen)

[1]Related to collectively organized systems of health care delivery and financing, [2]and a dilemma, resulting from the absence of the one compelling, integrating "grand theory"? – cf. Thomas Nagel: *The Fragmentation of Value* (1979) ; source of this chart: M. Schlander (2005): *Economic evaluation of medical interventions: answering questions people are unwilling to ask?* Paper presented to the International Health Economics Association (iHEA) 5th World Congress, Barcelona, Spain, July 9-15, 2005.

Analysis

Values Talk: A Tower of Babel ?[1]

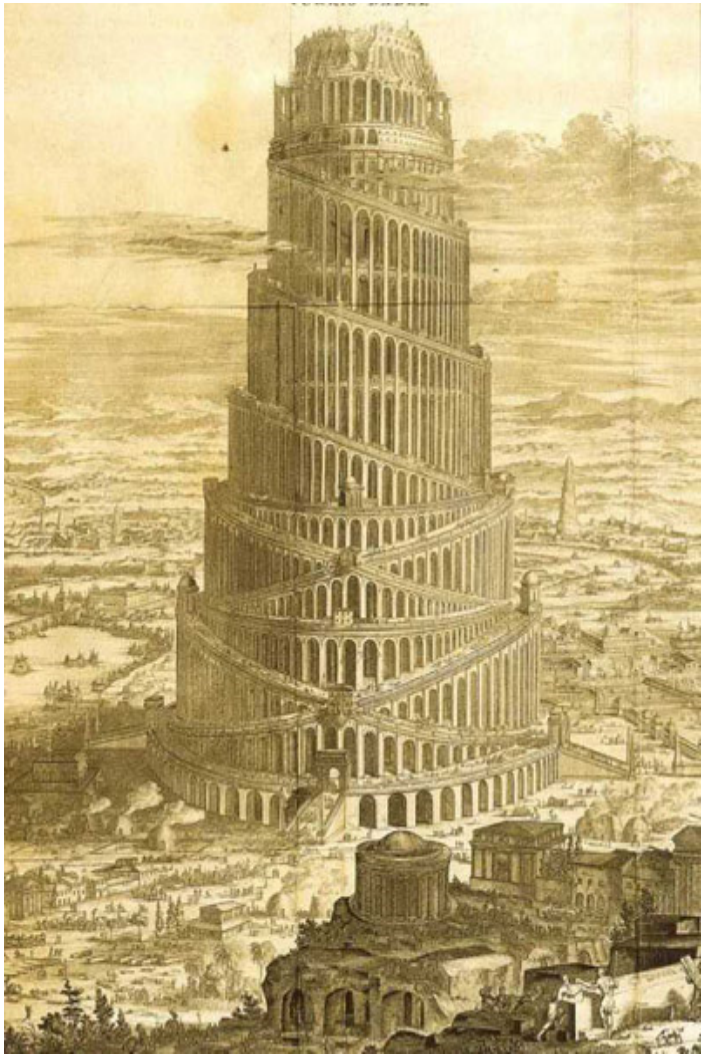


Illustration by Athanasius Kircher

Referral to many different and often incommensurate things…

A key paradox:

The discourse about values is both very important and very ambiguous…

Stakeholders may be tempted to react to this problem with either

reductionism
(focusing on one particular definition of values to the neglect of other relevant types)

or

nihilism…
(either rejecting all values analyses as equally unreliable, or accepting all as equally credible)

[1]M. Giacomini et al. (2004)

Consensus

Vertical versus Horizontal Equity

Rights as Goals:

- "To fail to satisfy people's basic needs and provide essential skills and opportunities is to leave people without recourse, and people without recourse are not free."
  (A. Sen, 1984; C. Korsgaard, 1993)
- Vertical equity as "positive discrimination" (cf. G. Mooney, 2000)

Relevant Legal Provisions:

- Human Rights Legislation
- Constitutional Provisions (…)
- Nondiscrimination and Rights of Persons with Disabilities
- EU Disability Legislation
- UK Equality Act
- …

Consensus

Empirical Ethics

The "Sharing Perspective":

A Broad Range of Social Preferences

- severity of the initial health state,
  i.e., a stable preference to prioritize health care for the worse off;
- urgency of the initial health problem,
  especially if life-threatening, i.e., the so called "rule of rescue";
- capacity to benefit of relatively lower importance,
  i.e., people appear to value additional health gains lower
  once a certain minimum effect has been achieved;
- certain patient attributes (such as [younger] age,
  parent or caregiver status, [non] smoker);
- a strong dislike for "all-or-nothing" resource allocation decisions;
- rights-based considerations (such as nondiscrimination).

Consensus

Potential Ways Forward

Evidence of Clinical Effectiveness:

- Approval based on surrogate endpoints should be accepted as an interim solution only.
- Conditional reimbursement to ensure rapid patient access may be linked to "coverage with evidence development" agreements.
- Even at prevalence rates as low as 1/50,000 (the URD qualifier), there would be about 10,000 patients in Europe.
- Thus it should be possible to set up multinational RCTs designed to show relevant clinical endpoint benefit.
- If necessary, such trials might be supported by the not-for-profit *European Clinical Research Infrastructure Network* (ECRIN).

Consensus

Potential Ways Forward

Perspectives on Cost:

- From a decision-makers' perspective, overall budgetary impact should be more relevant than incremental cost effectiveness ratios.
- If a social value perspective (instead of an almost exclusive focus on individual utility) was adopted, the social opportunity cost (or [social] value foregone) of adopting a program would be reflected by its net budgetary impact. This would move the focus from cost per patient to cost on the program level.
- Likewise, a pragmatic approach would reflect the commercial realities and the basic cost structure of the research-based biopharmaceutical industry, which incidentally is showing signs of a strategic shift from price maximization to life cycle revenue management (in order to "extract" maximum value).

Consensus

Potential Ways Forward

Valuation Principles:

- **Alternative** economic (e)valuation principles – that promise to reflect normative concerns and capture social preferences better than the conventional logic of cost effectiveness – should be rigorously assessed for their potential to complement of replace the currently predominant standard.
- **Candidates** include (but are not limited to)
  - cost value analysis, using the person-trade off or the relative social willingness-to-pay method;
  - a multicriteria decision analysis framework, which, in principle, might incorporate cost utility analysis with benchmarks adjusted to multiple contextual variables;
  - the use of alternative methods to value benefit.

Thank You for Your Attention!

on behalf of the authors:

Professor Michael Schlander, M.D., Ph.D., M.B.A.

Contact

www.innoval-hc.com
www.michaelschlander.com

michael.schlander@innoval-hc.com
michael.schlander@medma.uni-heidelberg.de

INNOVAL HC
Institute for Innovation & Valuation in Health Care

Address

An der Ringkirche 4
D-65197 Wiesbaden / Germany

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The full Consensus Document will be made available for download at the Institute's website, **www.innoval-hc.com**