UNIVERSITÄT
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Interventions for Ultra-Rare Disorders (URDs)

How to Assess “Value for Money”?

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INNOVAL HC
Institute for Innovation & Valuation in Health Care

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

Abstract

Interventions for Ultra-Rare Disorders (URDs): How to Assess "Value for Money"?

Schlander M, Garattini S, Holm S, Kolominsky-Rabas P, Nord E, Persson U, Postma M, Richardson J, Simoens S, de Solà-Morales O, Tolley K, Toumi M

Background: Given the economics of biopharmaceutical research and development (R&D), characterized by substantial fixed and often low variable (volume-dependent) cost, many drugs for ultra-rare disorders (URDs) fail to meet widely used benchmarks for cost effectiveness.

Objectives: To identify key issues arising when interventions for URDs are subjected to formal Health Technology Assessments (HTAs), and to deliberate potential solutions.

Methods: An international group of clinical and health economic scholars met twice in conjunction with Annual European ISPOR Congresses in November 2012 and in November 2013.

Results: The group reached consensus that the complexities of R&D of new treatments for URDs may require conditional approval and reimbursement policies, but this should not be used as a justification for showing surrogate endpoint improvement only. Strong evidence of clinical effectiveness should be expected within reasonable timeframes. In contrast to well-established principles of evidence-based medicine, the logic of cost effectiveness (including benchmarks for incremental cost per quality-adjusted year, QALY, applied by some agencies as a measure of "value for money") does not adequately capture prevailing social norms and preferences regarding health care resource allocation. Such preferences include, but are not limited to, a priority for care for the worst off (related to initial health state), for those with more urgent conditions (the so called "rule of rescue"), and a relatively lower priority based upon capacity to benefit, as well as a dislike against "all or nothing" resource allocation decisions that might deprive certain groups of patients from any chance to access effective care.

Conclusions: There is a strong need for an improved paradigm to determine value for money. Promising candidates include direct social value measurement using the relative social willingness-to-pay or person trade-off instruments, and a greater role for budget impact analysis. As a pragmatic alternative, multi-criteria decision analysis may be useful as a tool for assessment.

Available for download at www.innoval-hc.com.

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)

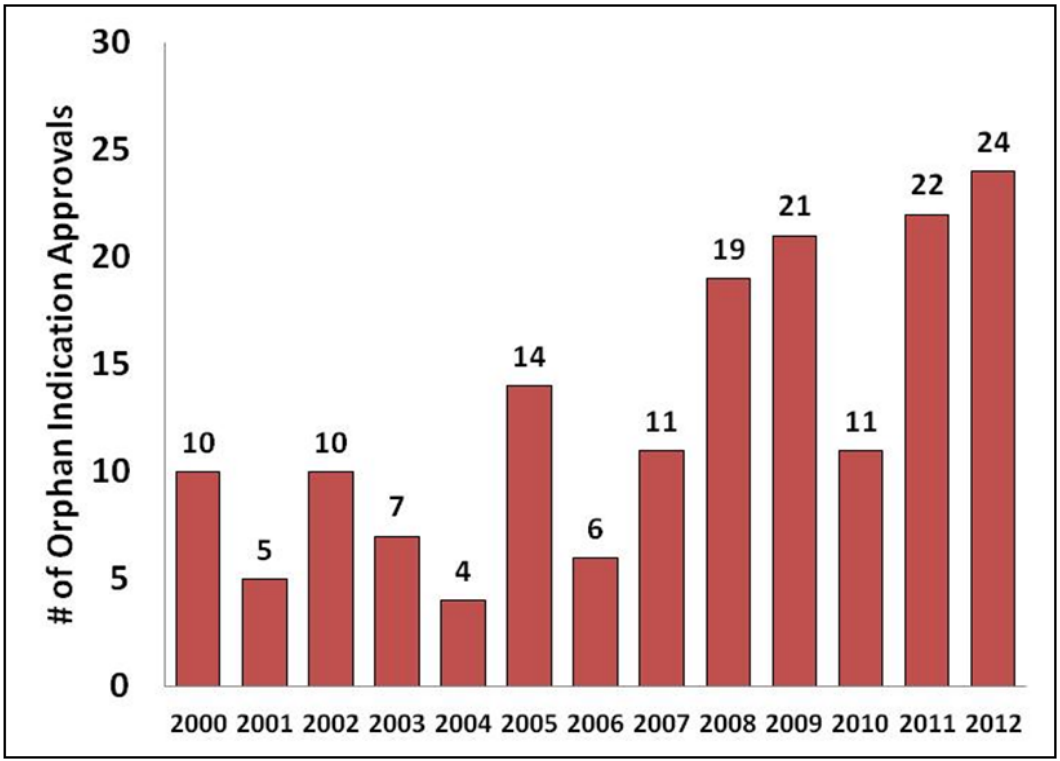
Some Measures:

- 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

Impact of Orphan Drug Legislation



Source: http://www.biotech-now.org/wp-content/uploads/2013/03/Historic-Orphan-Drug-Approvals.png

The 5 Most Expensive Drugs in the World[1]

1. **Soliris (Alexion)**
   paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS); average annual cost: **US-$ 409,500**
2. **Elaprase (Shire)**
   Hunter syndrome (ERT); **US-$ 375,000** p.a.
3. **Naglazyme (BioMarin)**
   mucopolysaccharidosis (MPS) VI (ERT); **US-$ 365,000** p.a.
4. **Cinryze (ViroPharma)**
   hereditary angioedema (HAE); **US-$ 350,000** p.a.
5. **Myozyme (Sanofi / Genzyme)**
   Pompe disease (ERT); **US-$ 300,000** p.a.

[1]S. Williams, The Motley Fool, June 29, 2013. http://www.fool.com/investing/general... [last accessed Jan. 22, 2014]

Clinical Effectiveness

Clinical evidence for orphan medicinal products a cause for concern?

Eline Picavet, David Cassiman, Carla E Hollak, Johan A Maertens, Steven Simoens

[…]

We quantitatively assessed the characteristics and quality of clinical evidence of the pivotal studies of 64 OMPs as described in the European Public Assessment Report and/or the Scientific Discussion document prepared by the Committee for Human Medicinal Products of the EMA.

[…]

The 64 OMPs were altogether authorized for 78 orphan indications, for which 117 studies were identified as 'pivotal' or 'main' studies. In approximately two thirds of the studies, the allocation was randomized (64.8%) and a control arm was used (68.5%). Half of the studies applied some type of blinding. Only a minority (26.9%) of the studies included a Quality-of-Life (QoL) related endpoint, of which a third claim an improvement in QoL.

[…]

In conclusion, the pivotal studies that are the basis for marketing authorization of OMPs are a cause for concern, as they exhibit methodological flaws […]

Orphanet Journal of Rare Diseases 2013, 8: 164

Clinical Effectiveness

Systematic review of available evidence on 11 high-priced inpatient orphan drugs

Tim A Kanters, Caroline de Sonneville-Koedoot, W Ken Redekop, Leona Hakkaart

[…]

A systematic review was performed […] for 11 inpatient orphan drugs listed on the Dutch policy rule on orphan drugs. For included studies, we determined the type of study and various study characteristics.

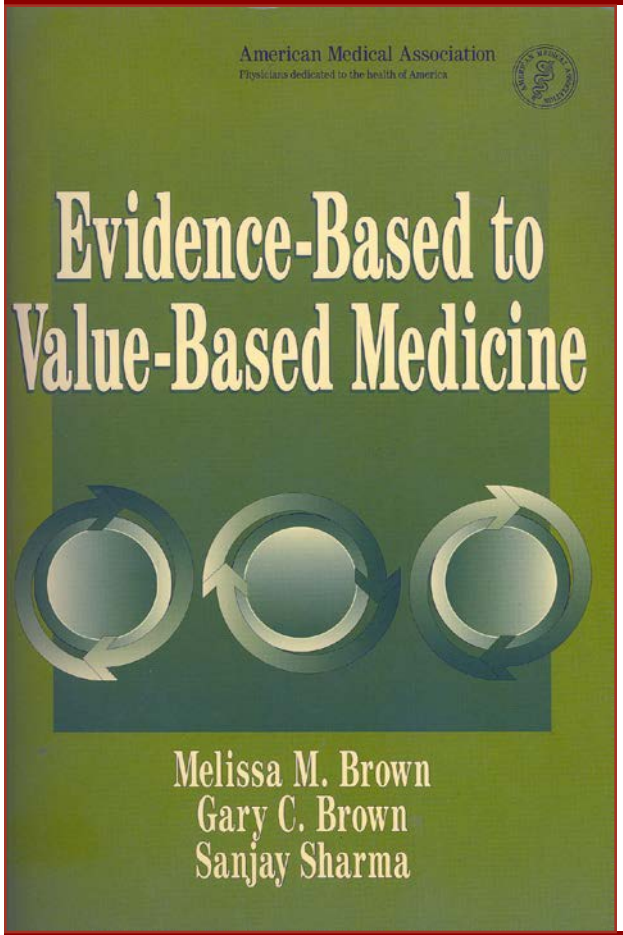
[…]

A total of 338 studies met all inclusion criteria. Almost all studies (96%) focused on clinical effectiveness of the drug. Of these studies, most studies were case studies (41%) or observational studies (39%). […] a randomized clinical trial was available for 60% of the orphan drugs. Eight studies described the cost-effectiveness of an orphan drug; an equal number described an orphan drug's budget impact.

[…]

Despite the often heard claim that RCTs are not feasible for orphan drugs, we found that an RCT was available in 60% of orphan drugs investigated. Cost-effectiveness and budget impact analyses for orphan drugs are seldom published.

Orphanet Journal of Rare Diseases 2013, 8: 124



- **Both rely on 'best available clinical evidence'**

  – however, applying different conceptual frameworks:

- **Opportunity cost and allocative efficiency**

  Interpersonal comparisons **!**

- **Need to capture all relevant consequences** (costs, effects)

  Time span beyond RCT data **!**

- **Need to capture real-life performance**

  Relevance of real-world studies **!**

  Cross-design synthesis **!**

- **Need to have a 'universal and comprehensive' measure of clinical [?] benefit**

  Loss of relevant information **?**

Economic Welfare Theory:

Value & Valuation: Utility

"Political economy has to take as the ***measure of utility*** of an object the maximum sacrifice which each consumer would be willing to make in order to acquire the object

...

the only real utility is that which people are *willing to pay* for."[1]

Contemporary Textbooks of Microeconomics:

"The **value** [of a product] to a given consumer is defined as the maximum amount that the consumer would be **willing to pay** for that [product]."[2]

[1] **Jules Dupuit (1844)**
De la Mesure de l'Utilité des Travaux Publiques. *Annales des Ponts et Chaussees* 1844; 2: 8.
Reprint: *International Economic Papers* 1952, 2: 83-110.

[2] Steven E. Landsburg: *Price Theory and Applications*, 5th ed., Mason, OH: South-Western 2002, p. 238.

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**

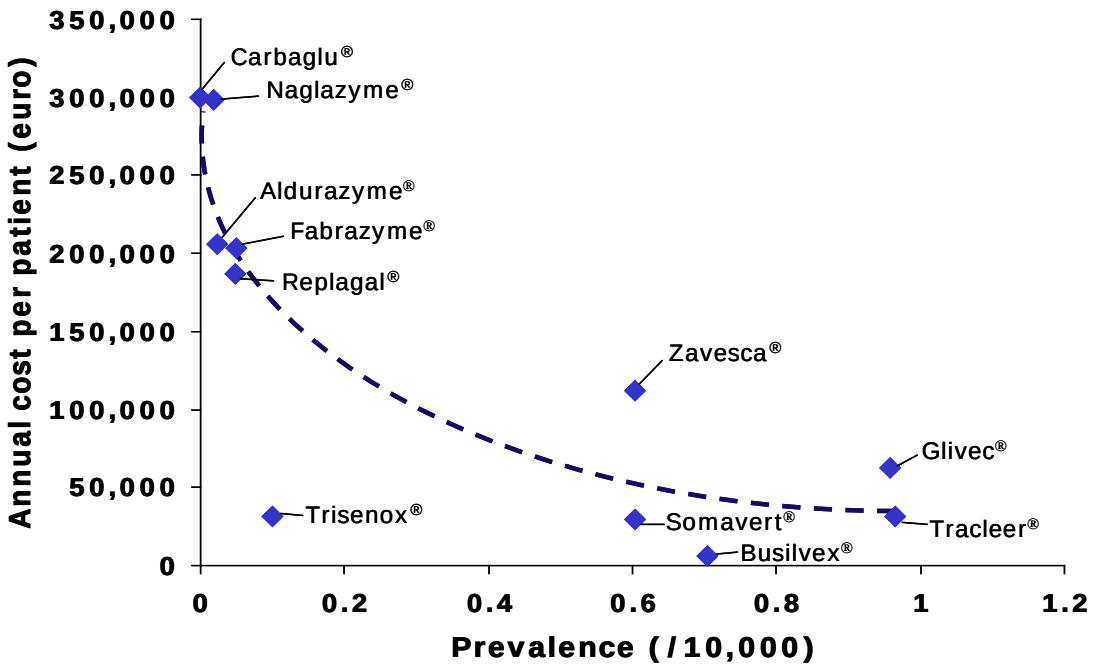
[1]C. Pritchard (2002); QALY: "quality-adjusted life year"; [2]George et al. (2001); LYG: "life year gained"
[3]D.M. Cutler, M. McClellan (2001); [4]A. Laupacis et al. (1992)

Some ICER Estimates 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)

Prevalence and Cost per Patient



Orphan drugs and the NHS: should we value rarity?

Christopher McCabe, Karl Claxton, Aki Tsuchiya

The growing number and costs of drugs for rare diseases are straining healthcare budgets. Decisions on funding these treatments need to be made on a sound basis

[…]

The justification for special status for rare diseases must rest on the question: should we value the health gain to two individuals differently because one individual has a common disorder and the other has a rare disorder?

[…]

While orphan drugs were rare, healthcare systems were able to deal with them in an ad hoc manner. But there are now over 6000 orphan diseases with over 200 treatments approved by the US Food and Drugs Administration and 64 trials currently sponsored by the US Office of Orphan Products Development. […] Genomics is expected to disaggregate currently prevalent diseases into many genetically defined distinct conditions. Orphan status is thus likely to become increasingly common.

[…]

Special status for orphan drugs in resource allocation will avoid difficult and unpopular decisions, but it may impose substantial and increasing costs on the healthcare system. The costs will be borne by other, unknown patients, with more common diseases who will be unable to access effective and cost effective treatment as a result.

British Medical Journal 2005, 331: 1016-1019

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?

An Alternative Premise

"**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)**

How to Evaluate Interventions for URDs?

- **Two International Expert Workshops**
  - in conjunction with Annual European ISPOR Congresses in Berlin / Germany, November 08, 2012, and in Dublin / Ireland, November 07, 2013
  - supported by BioMarin and a second biopharmaceutical company 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 promising ways forward, overcoming the shortcomings of currently prevailing evaluation paradigms

[1]Alexion (2012) and Genzyme (2013), respectively

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;
  - …

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 rhis chart: M. Schlander (2005): *Economic evaluation of medical interventions: answering questions people are unwilling to ask?* Paper presented to the International Health Eco nomics Association (iHEA) 5th World Congress, Barcelona, Spain, July 9-15, 2005.

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
- …

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).

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 alone.
- 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).

Potential Ways Forward

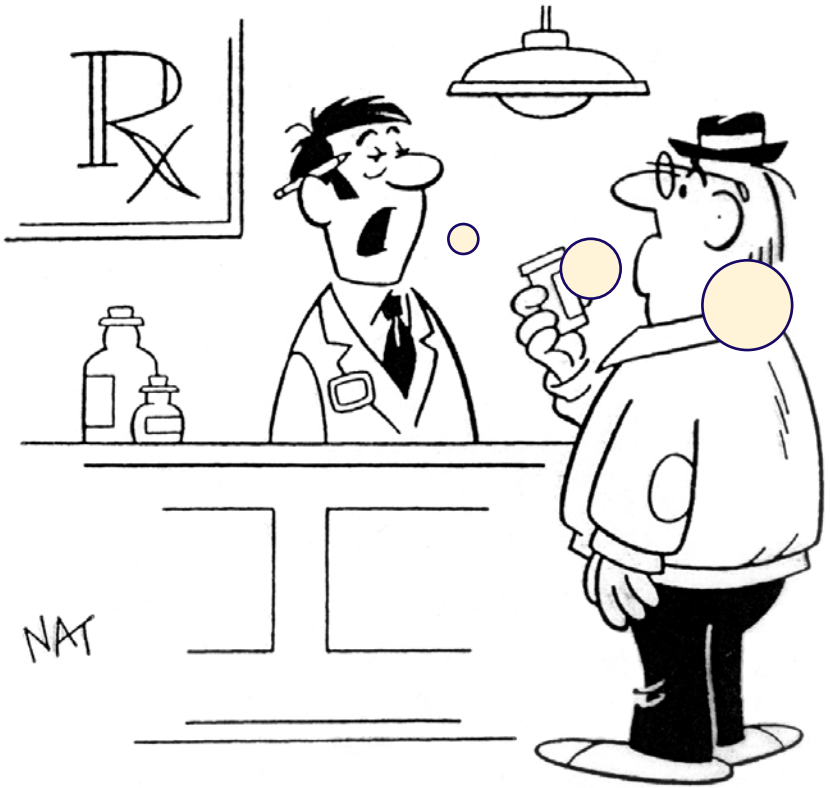
Perspectives on Cost:

- 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).

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.
- The most promising **candidates** include (but are not limited to)
  1. a multicriteria decision analysis (MCDA) framework, which, in principle, might incorporate cost utility analysis with benchmarks adjusted to multiple contextual variables, as a short-term or "quick" fix;
  2. cost value analysis, using the person-trade off (PTO) or the relative social willingness-to-pay (RS-WTP) method, as a mid- to long-term solution better capturing **social value**.



"The drug itself has no side effects – but the number of health economists needed to prove its value may cause dizziness and nausea."

Thank You for Your Attention!

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

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The URD Consensus Document is accessible at the Institute's website, **www.innoval-hc.com**