UNIVERSITÄT HEIDELBERG

Game Changers in Research: Session on "*Sustainable Research and Affordable Therapies to Maintain Our Orbit*"

The European Social Preferences Measurement Study (ESPM) Project

Rationale: The Economics of R&D, Life Cycle Revenue Management, Cost per Patient Treated, Budgetary Impact, Social Cost Value Analysis

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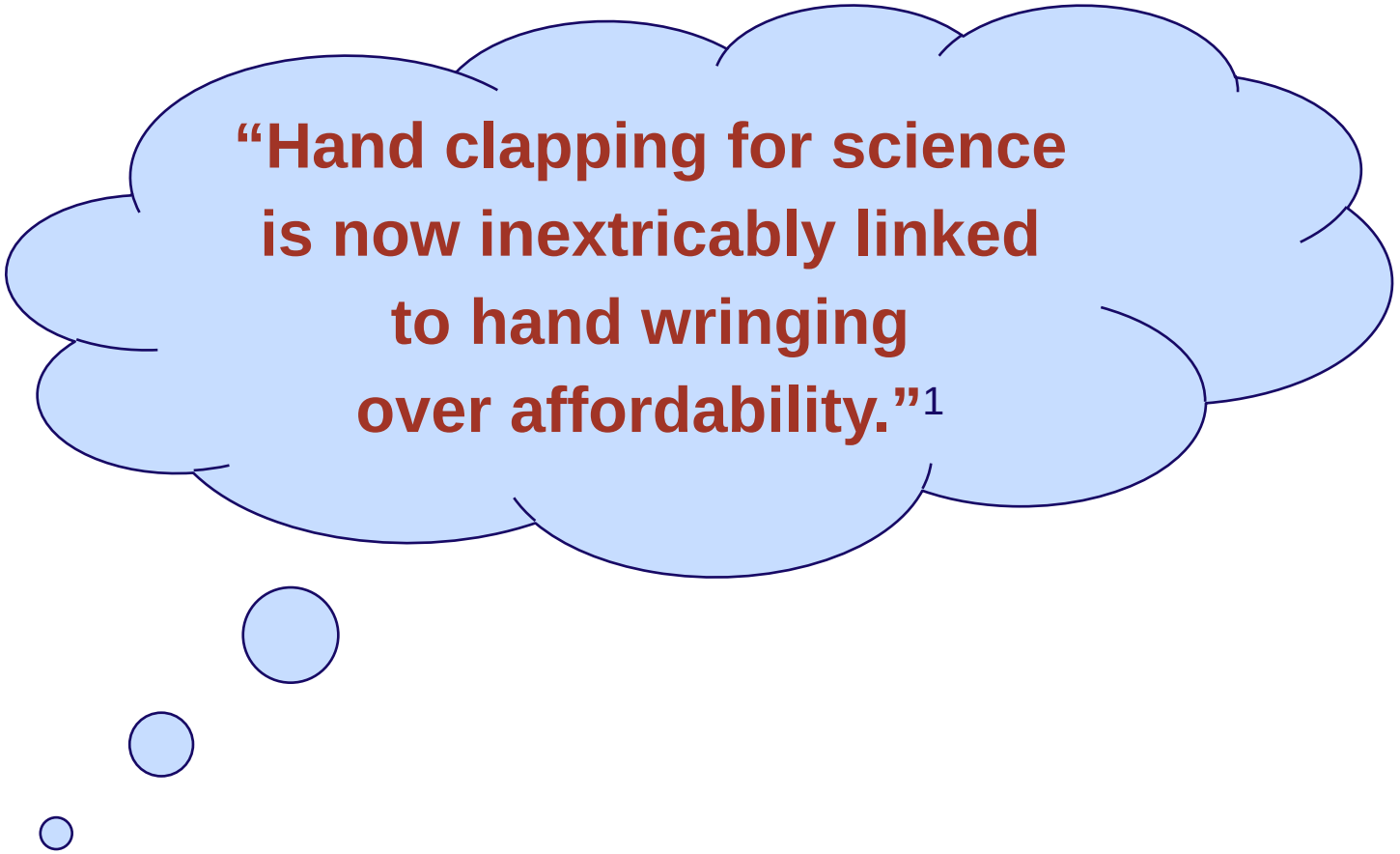
on behalf of the URD / ESPM Study Group

INNOVAL HC
Institute for Innovation & Valuation in Health Care

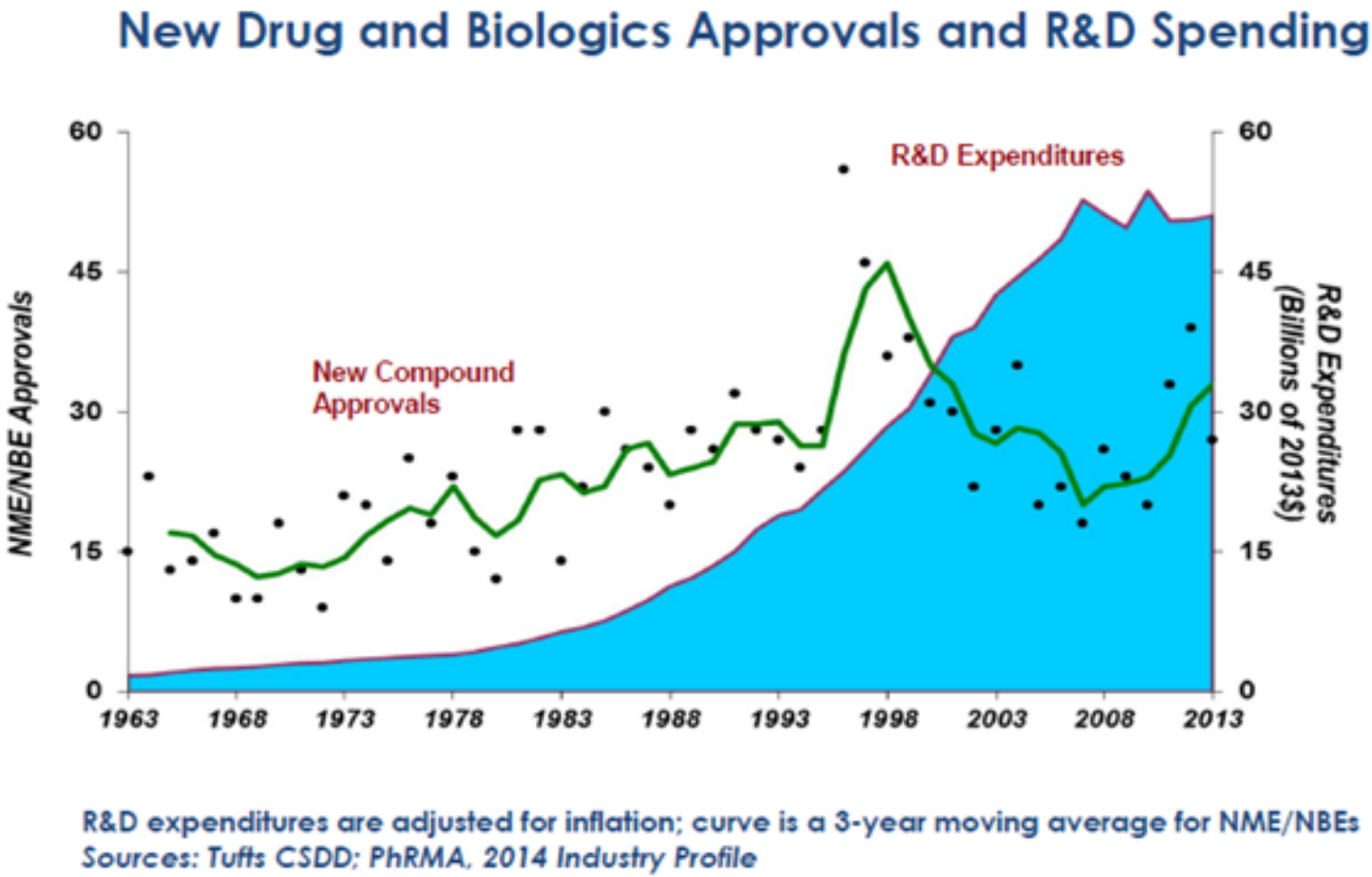
8th European Conference on Rare Diseases & Orphan Products (ECRD)
Edinburgh / Scotland, May 28, 2016, 14:30h - 16:00h

& Mannheim Medical Faculty, University of Heidelberg – www.medma.uni-hd.de



[1] **Peter B. Bach**
New England Journal of Medicine 2015 (November 05); 373 (19): 1797-1799.

The Social Value of OMPs: Rationale of the **ESPM** Study Project



Source: J.A. DiMasi. "*Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*", Tufts Center for the Study of Drug Development, November (2014). Available: at http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study, s.l.: s.n.

Pharmaceutical R&D:
Determinants of Fully Allocated R&D Cost / NME

- **Out-of-pocket costs**
  - Clinical development
  - Preclinical research & development
  - Discovery research
- **Clinical success and attrition r**ates
- **Capitalization**
  - Development Times ("Time-to-Market", TTM)
  - Cost of Capital

NME: New Molecular Entity

Pharmaceutical R&D: Fully Allocated Cost / NME

Study Reference	Sample of New Molecular Entities	Cost of Capital (real)	Discovery Research (included?)	Geography	Estimated cost of R&D [US$m, 2011 prices]
Hansen, 1979	First tested in humans between 1963 and 1975	8%	No	USA	**199**
Wiggins, 1987	1970-1985	8%	No	USA	**226**
DiMasi et al, 1991	First tested in humans between 1970 and 1982	9%	Yes (estimated)	USA	**451**
OTA, 1993	-	-	-	-	**625**
Myers and Howe, 1997	-	-	-	-	**664**
DiMasi et al, 2003	First tested in humans between 1983 and 1994	11%	Yes (estimated)	USA	**1,031**
Gilbert, Henske and Singh, 2003	Estimated first tested in humans between 1995 and 2002	-	Yes	Global	(1995–2000) **1,414** (2000–2002) **2,185**
Adams and Branter, 2006	Drugs entering human clinical trials for the first time 1989-2002	11%	Use DiMasi et al 2003	Global	**1,116**
Adams and Branter, 2010	Drugs entering human clinical trials for the first time 1989-2002	11%	No	Global	**1,560**
Paul et al, 2010	Estimated 1997-2007	11%	Yes	Global	**1,867**
Mestre-Ferrandiz et al, 2012					**1,506**
DiMasi, 2014					**2,600 †**

Adapted from: J. Mestre-Fernandiz, J. Sussex and A. Towse. *The R&D Cost of a New Medicine.* London: Offiice of Health Economics (OHE).
†J.A. DiMasi. *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, Tufts Center for the Study of Drug Development (2014).

Specific Challenges for (Ultra-)Rare Disorders

- **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;
  - …

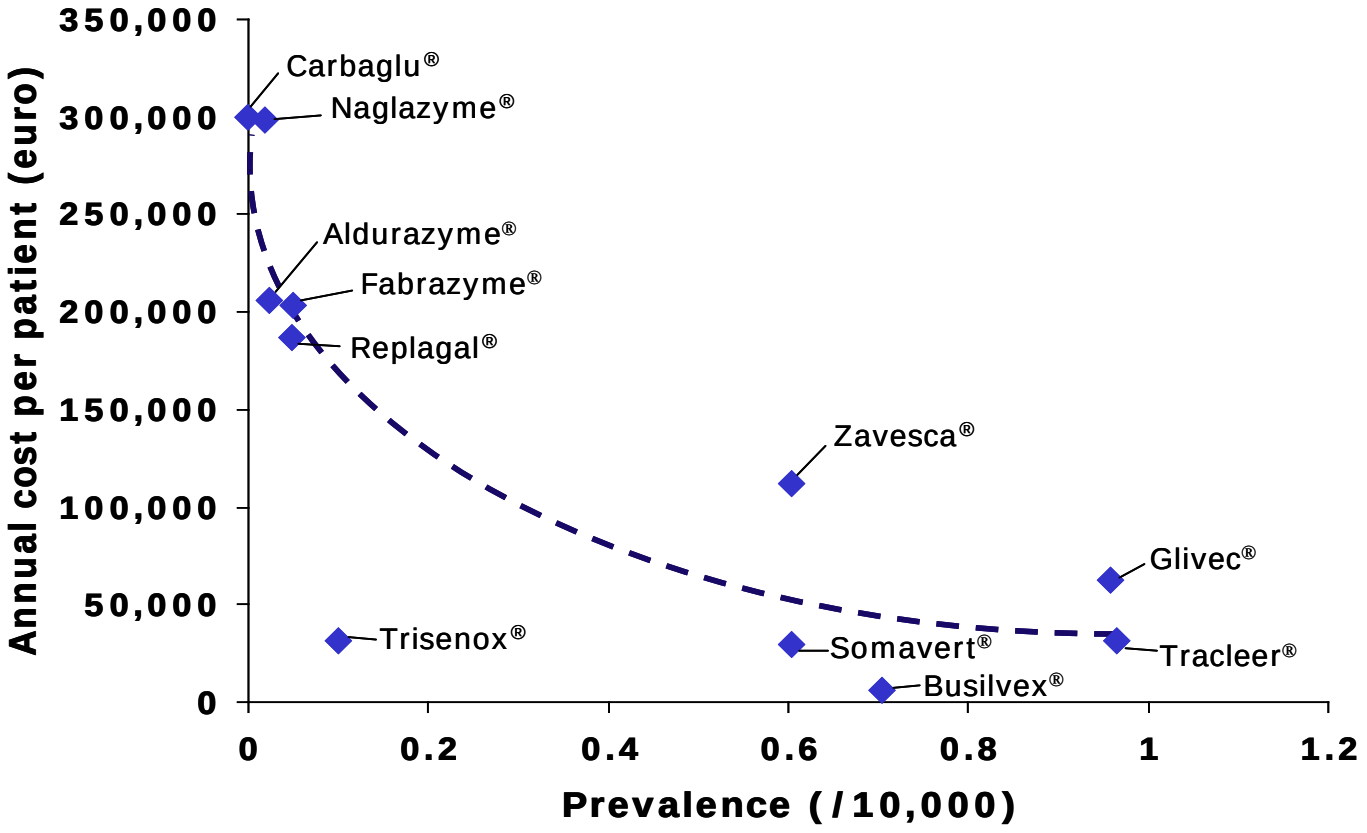
[1]M. Schlander, S. Garattini, P. Kolominsky-Rabas et al. *Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). Consensus Statement based upon an International Expert Workshop*. Wiesbaden , July 19, 2013.

Specific Challenges for (Ultra-)Rare Disorders

- **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;
  - …

[1]M. Schlander, S. Garattini, P. Kolominsky-Rabas et al. *Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). Consensus Statement based upon an International Expert Workshop*. Wiesbaden , July 19, 2013.

Prevalence and Cost per Patient



M. Schlander and M. Beck, *Current Medical Research & Opinion* 2009; 25 (5): 1285-1293

"Departures from a strict utilitarian perspective would have to justified…"[1]

Utilitarian Thought

- **John Stuart Mill (1806-1873):**

  "What is best brings the greatest good for the greatest number"

- **Jeremy Bentham (1748-1832):**

  "The greatest happiness of all those whose interest is in question is the right and proper, and the only right and proper and universally desirable, end of human action."

Medical Utilitarianism

- A variant of act utilitarian thought, **exclusively focusing on individual health outcomes** (usually *QALYs*)

[1]M. Drummond, A. Towse, *European Journal of Health Economics 2014, 15: 335-340*

Key Assumptions of the Conventional Logic

Quality-Adjusted Life Years (QALYs)

- (fully) capture the value of health care interventions;
- are all created equal ("a QALY is a QALY is a QALY…").

Maximizing the number of QALYs "produced"

- ought to be the primary objective of collectively financed health schemes,
- leading to the concept of thresholds (or benchmarks) for the maximum allowed cost per QALY gained.

Decreasing cost per QALY

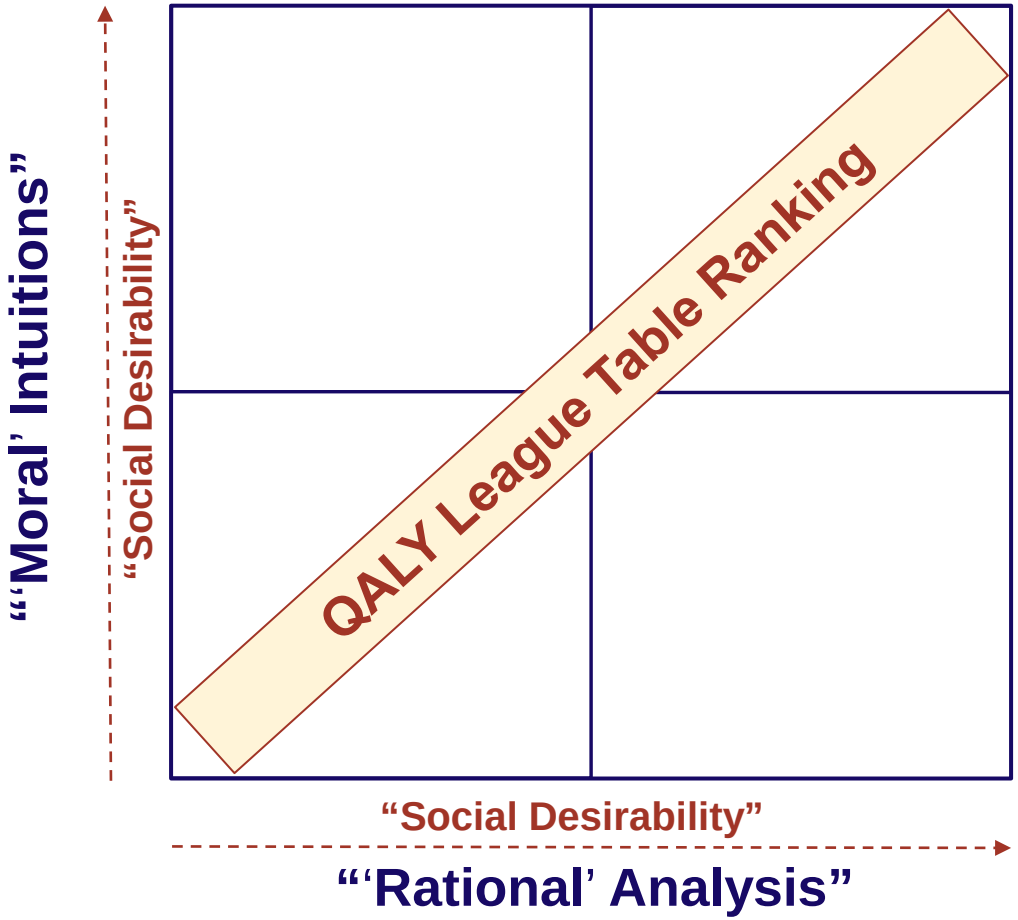
- implies increasing social desirability of an intervention.

Textbook Example: "QALY League Table"[1]

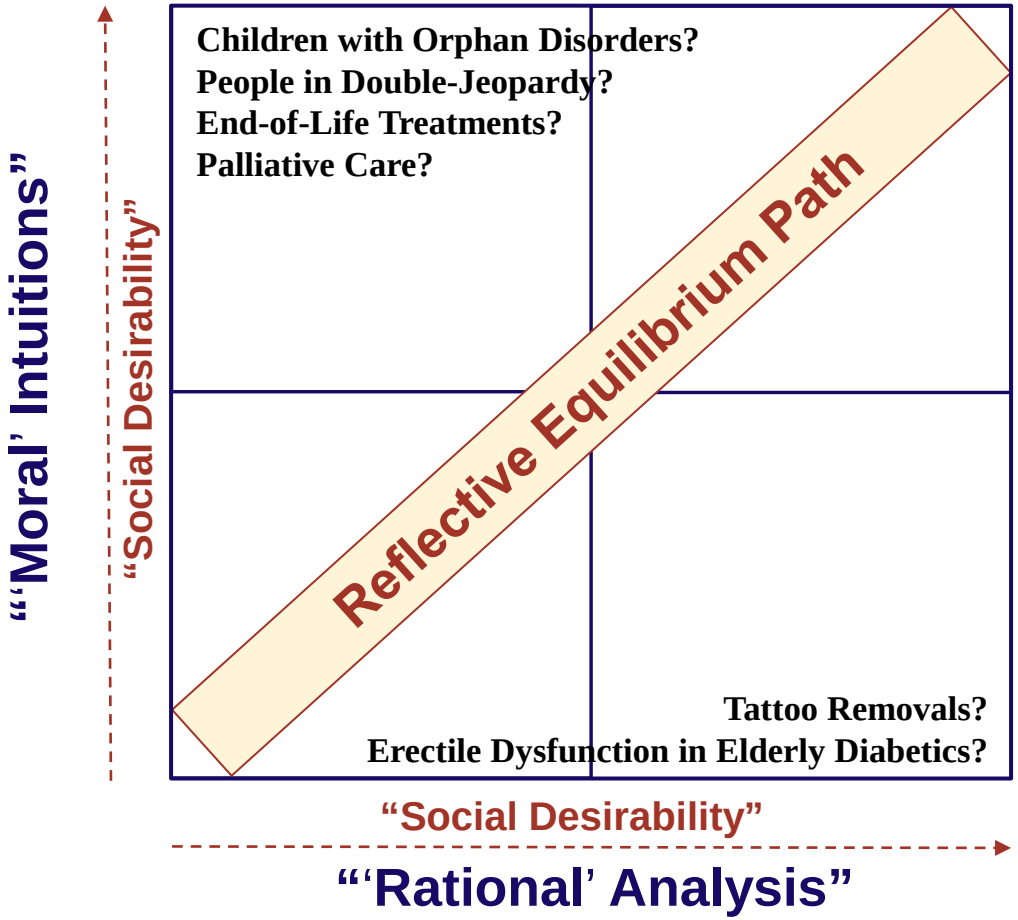
Ranking [original]	**Intervention** [abbreviated; comparator not stated in original table]	**Cost / QALY [£ (1990)]**
3	G.p. advice to stop smoking	£ 270
5	Antihypertensive therapy to prevent stroke	£ 940
6	Pacemaker implantation	£ 1,100
7	Valve replacement for aortic stenosis	£ 1,140
8	Hip replacement	£ 1,180
9	Cholesterol testing and treatment	£ 1,480
11	Kidney transplant	£ 4,710
12	Breast cancer screening	£ 5,780
15	Home hemodialysis	£ 17,260
18	Hospital hemodialysis	£ 21,970
20	Neurosurgery for malignant intracranial tumors	£ 107,780
21	Epoetin alfa therapy for anemia in dialysis patients	£ 126,290

[1]A. Maynard. *Economic Journal* 1991; 101 (408): 1277-1286

Reflective Equilibrium



Reflective Equilibrium



What's Wrong with the Conventional Logic?

Effectiveness and Efficiency

- by definition, "efficiency" is a secondary or instrumental objective,
- whereas the "effectiveness" criterion invariably represents the primary objective.

Efficiency

Need to distinguish between

- technical efficiency, productive efficiency, and allocative efficiency;
- static and dynamic efficiency.

Social Value ("Utility")

Existence of

- components different from individual utility and its aggregation;
- social (i.e., non-selfish) preferences, rights and duties.

Perspectives on Value

A Broad Range of Empirical (/ Non-Selfish) **Preferences** indicating objectives apart from simple QALY maximization:

Prioritization criteria supported by empirical evidence include

- **severity** of the initial health state,
- **urgency** of the initial health problem,
- **capacity to benefit** of relatively lower importance,
- certain **patient attributes**,
- a strong dislike for "**all-or-nothing**" resource allocation decisions,
- a "**sharing**" perspective (with less emphasis on cost per patient),
- and **rights**-based considerations.

A Changing Perspective on Cost

- A **decision-makers**' perspective:

  overall **budgetary impact** (*transfer cost*)

- A **social value** perspective:

  (instead of an almost exclusive narrow focus on individual utility and its aggregation):

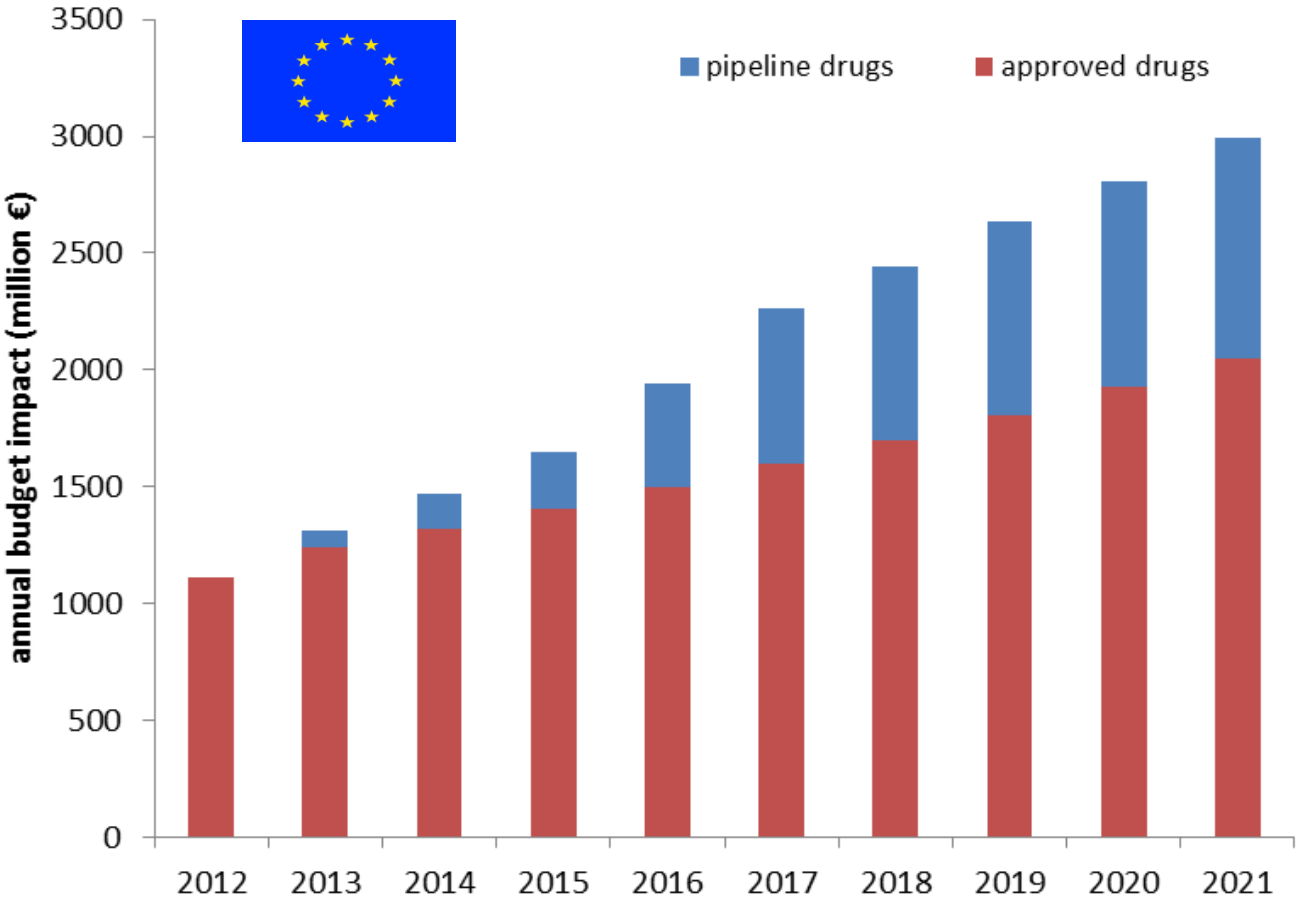
  social **opportunity cost** (or [social] value foregone) better reflected by net budgetary impact (*transfer cost*):

  Moving focus from cost per patient to cost at program level

- A **pragmatic** perspective:

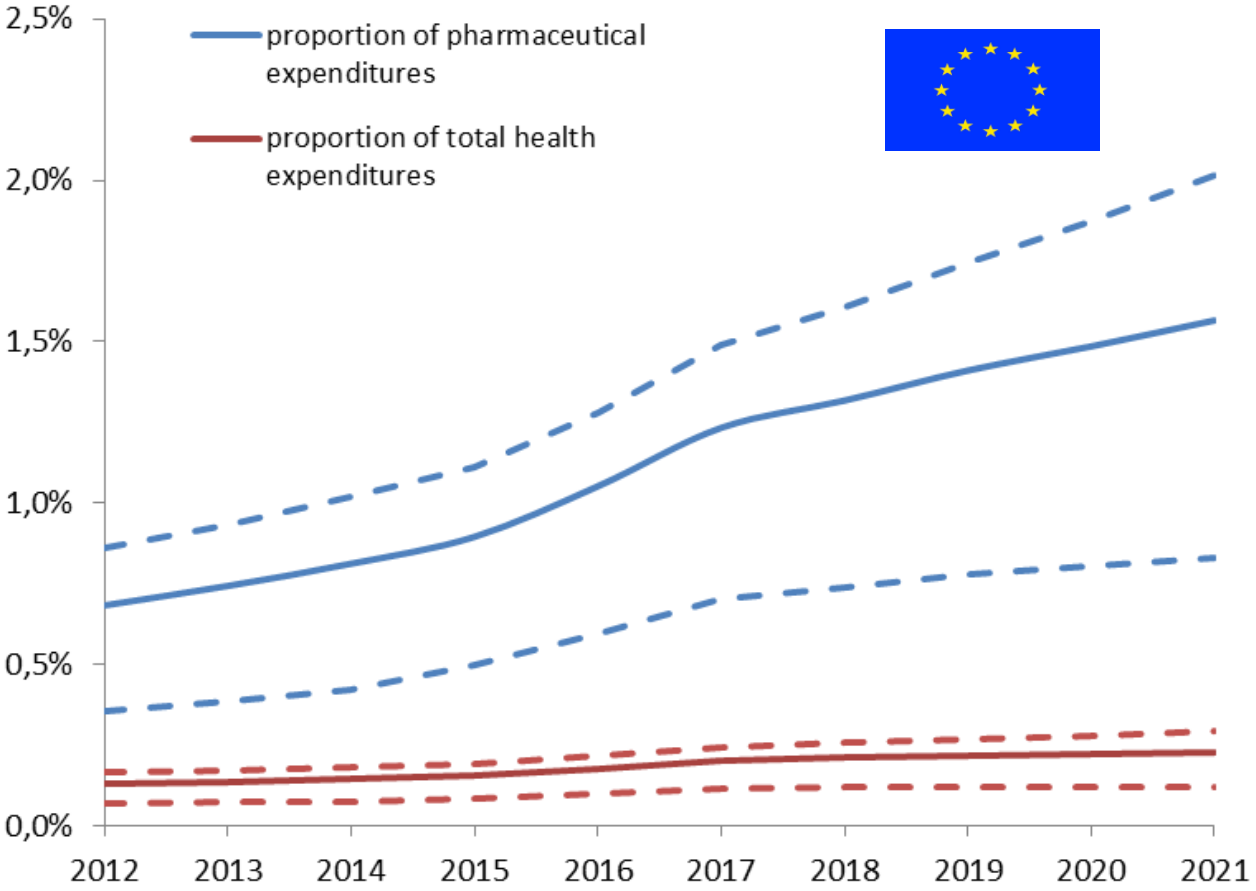
  should reflect the commercial realities of the research-based biopharmaceutical industry, which is showing signs of a shift from price maximization to **life cycle revenue management**.

Projected URD Budget Impact



Annual budget impact of approved and pipeline drugs for ultra-rare diseases over 10 years (2012 to 2021) in Europe from a payer's perspective (Schlander et al., 2014).

Projected URD Budget Impact



Proportion of pharmaceutical and total health expenditures in Europe spent on drugs for ultra-rare diseases (URDs). Dashed lines indicate ranges provided by the extreme-case scenario analyses. Source: Schlander et al. (2014).

Elements of a Roadmap

towards **Social Cost Value Analysis (SCVA)**, better approximating the public's expectations

Multi-Criteria Decision Analysis (MCDA)

- including a more prominent role for budgetary impact

Social Preferences Measurement Project

- generating more robust empirical evidence on "social preferences"
- in an inclusive effort, inviting multiple stakeholders to participate (cf. the example of www.**SwissHTA**.ch)

Research Need

- Many studies of social preferences …
  - most of them small
  - many studies limited in scope
  - many studies likely to be impaired by framing effects
  - other study types (not choice-based experiments)
  - some studies of questionable methodology
- … very difficult to generalize
  - severity probably best documented contextual variable
  - distinct difficulties to quantify effects observed
  - if measures of willingness-to-pay were incorporated, they typically reflected maximal individual WTP
  - social willingness-to-pay in exchange for health care programs covered under a collectively financed health scheme might be more relevant

ESPM Project: Research Objectives

1. To investigate systematically how the general public valuates selected characteristics ("attributes") of health care interventions,
   - ¬ and how they weigh them against each other (including their interaction).
2. To compare the valuation results obtained in the study with those based on the logic of cost effectiveness by means of a utility comparator.
3. To assess the sensitivity of weights to the level of information offered to respondents and to potential framing effects.
4. To identify international similarities and differences with regard to the valuation of the attributes tested.
5. (in Phase II:) to explore the agreement of respondents between their choices in the experimental setting, their policy implications, and their policy preferences.

ESPM Project: International Study Group

- **Silvio Garattini** (Mario Negri Institute, Milan / Italy)
- **Sören Holm** (U of Manchester / England)
- **Peter Kolominsky** (U of Erlangen / Germany)
- **Deborah Marshall** (U of Calgary / Canada)
- **Erik Nord** (U of Oslo / Norway)
- **Ulf Persson** (IHE, Lund / Sweden)
- **Maarten Postma** (U of Groningen / The Netherlands)
- **Jeffrey Richardson** (Monash U, Melbourne / Victoria)
- **Michael Schlander**[1] (U of Heidelberg / Germany)
- **Steven Simoens** (U of Leuven / Belgium)
- **Oriol de Sola-Morales** (IISPV, Barcelona / Spain)
- **Harry Telser**[1] (polynomics / Switzerland)
- **Keith Tolley** (Tolley HE, Buxton / England)
- **Mondher Toumi** (U of Lyon / France)

[1]Scientific Project Leaders

ESPM Project: Funding of Study Phase I

- under an unrestricted educational grant policy
- **SwissHTA stakeholders**:
  - **curafutura** (association of Swiss statutory health insurance [OKP] companies), Bern / Switzerland
  - **Galenica**, Bern /Switzerland *(t.b.c.)*
  - **Interpharma** (association of the Swiss research-based biopharmaceutical industry), Basel /Switzerland
  - **SVV** (*Schweizerischer Versicherungsverband*; association of Swiss private health insurance companies), Zürich / Switzerland
- **URD project sponsors**:
  - **BioMarin**, London / England
  - **Genzyme**, Naarden / Netherlands

ESPM Project: Characteristics Investigated[1]

1. **Severity** of the initial health state
   (i.e., *ex ante*, before intervention)
2. **Urgency** of an intervention
   (in order to avoid major irreversible health impairments)
3. **Uncertainty** of outcomes ("risk")
   (i.e., probability of effectiveness / consequences)
4. **Clinical effectiveness** (or consequences);
   health gain; length and quality of life
5. **Age** of patient (or "fair innings")
6. **Rarity** of disorder (or fair chance of access);
   i.e., prevalence or number of persons benefitting
7. **Cost** (from different perspectives; t.b.c.)

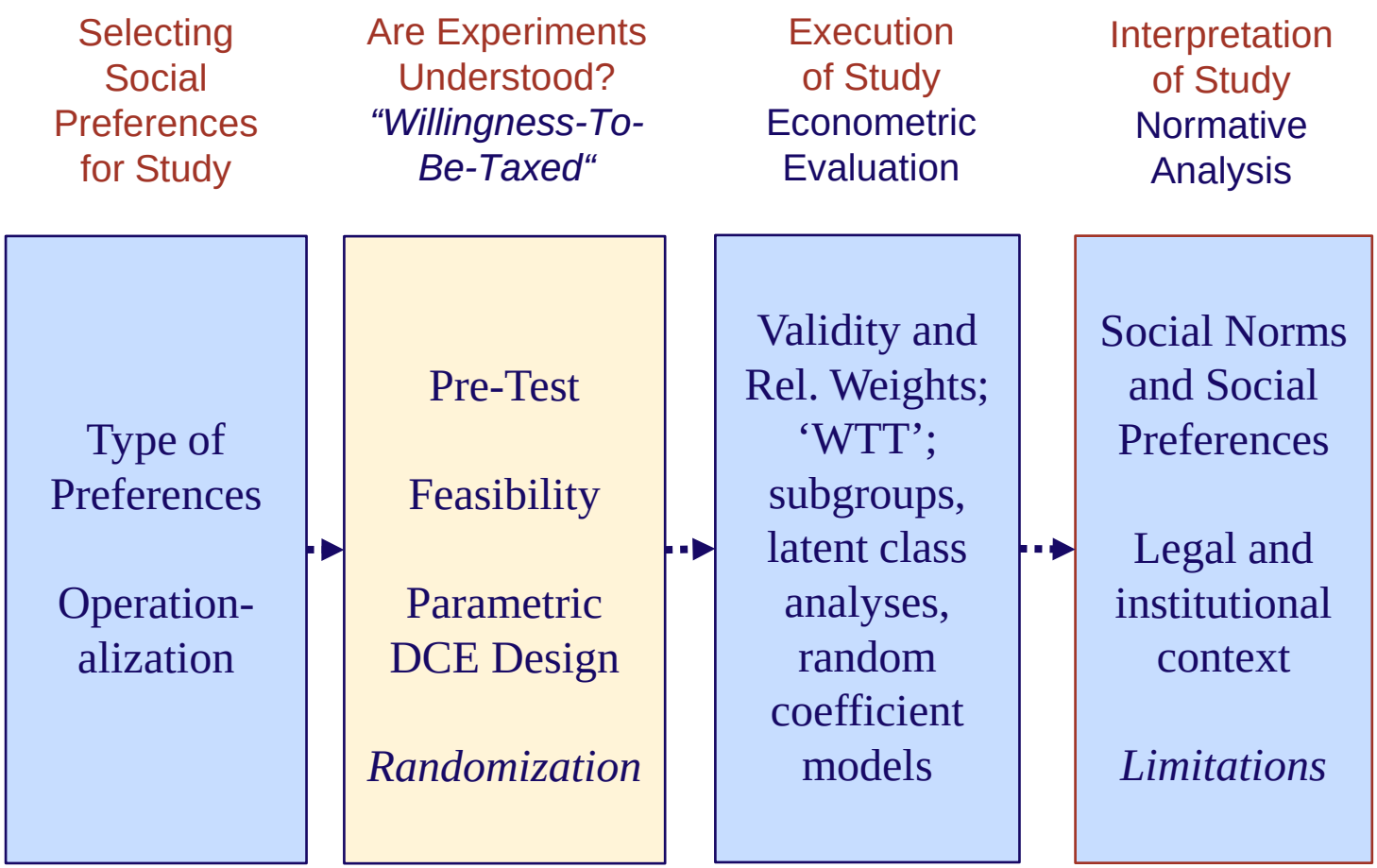
[1]Note that concept presented here reflects status as at Feb.04, 2016, and may undergo change and revision during subsequent Work Packages.

ESPM Project: Design Elements[1]

1. **Representative population sample(s)**
2. **Discrete Choice Experiment (DCE) design**
3. **Testing for framing effects** (primarily by randomization):
   - uncertainty (certain outcomes versus specified probabilities)
   - rarity (different levels of information on implications)
   - perspective on cost (cost per patient treated vs. cost per member of a collectively financed health scheme; "zero sum" assumption)
4. **Utility comparator**
5. **Testing for potential cognitive overload**
6. **Econometric evaluation**
   - analyzing subsamples
   - latent class and random coefficient models

[1]Note that concept presented here reflects status as at Feb.04, 2016, and may undergo change and revision during subsequent Work Packages.

ESPM: Major Steps in Study Phases I and II[1]



[1]Note that concept presented here reflects status V10 as at Feb.04, 2016, and may undergo change and revision during subsequent Work Packages.

ESPM Project: Who Will Benefit?

1. Health care decision-makers and payers

- seeking to incorporate the **social values of the population** covered by a collectively financed health scheme into priority-setting decisions;
- applying the **logic of cost effectiveness** with a serious interest in ist scope and ist limitations;
- interested in the exploration of the empirical rationale in favor of **alternative evaluation paradigms**, such as social cost value analysis;
- believing in the usefulness of **multi-criteria decision analysis** (MCDA) and seeking robst information on characetristics to be included in such frameworks, as well as their relative weights.

2. Policy-makers and stakeholders

- in Switzerland (Study Phase I)
- interested in the potential of increased international harmonization and integration of HTA process in Europe (Study Phase II)

3. Patients and R&D-based biopharmaceutical industry

Thank You for Your Attention!

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