UNIVERSITÄT HEIDELBERG

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Forschen für ein Leben ohne Krebs

Economical Perspectives in Rare Diseases

"A Paradigm Shift in Value Frameworks for Access"

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Key Elements of the Conventional Logic

Use value: 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…").

Aggregation: 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

Increasing Uneasiness with CE Thresholds

HTA Agencies

- NICE (England): end-of-life treatments, ultra-orphans
- TLV (Sweden): adjustments for severity

Research-Based Biopharmaceutical Industry

- Barriers to access
- Innovation (dealing with uncertainty and dynamic efficiency)

Payers

- NHS England: Cancer Drugs Fund
- A "prescription for uncontrolled growth in expenditures"[1]?

Academics

- Increasing literature on the importance of "other criteria"
- Scientific foundations of actual benchmarks for cost effectiveness: might be too high[2] / too low[3] / non-existent[4]?

[1]A. Gafni, S. Birch (1993)
[2]K. Claxton et al. (2013)
[3]M. Schlander et al. (2017)
[4]when social preferences are taken into account

Loopholes of the Conventional Logic

Effectiveness and Efficiency

Need to justify the appropriateness of the chosen effectiveness criterion

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

Efficiency

Need to distinguish explicitly 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 (and non-selfish) preferences; rights and duties.

Social Preferences – Definition as "Non-Selfish"[1]

A person exhibits social preferences if the person not only cares about the material resources allocated to her but also cares about the material resources allocated to relevant reference agents.[1]

In addition to material self-interest, these are

- **Reciprocity or Reciprocal Fairness**
  with fairness being determined by the equitability of the payoff distribution (relative to the set of feasible payoff distributions)
- **Inequity Aversion**
  resulting in altruism or envy towards other people
- **Pure Altruism**
  a form of unconditional kindness
- **Spiteful or Envious Preferences**
  always valuing a payoff of relevant reference agents negatively

Note heterogeneity of motives at the individual level and by context.

[1]cf. E. Fehr and U. Fischbacher (2002)

Social Preferences in the Economic Literature

"The taste for improving the health of others appears to be stronger than for improving other aspects of their welfare."[1]

[1]Kenneth Arrow (1921-2017)
Uncertainty and the Welfare Economics of Medical Care (1963; p. 954)

Valuation of Health: A Framing Issue?

1. **Use value** (consumer perspective)
2. **Option value** (due to uncertainty and risk averse citizens)
3. **Externalities** (caring externalities and altruistic behaviors)

Perspective on incremental costs and WTP:

1. direct out-of-pocket payments
2. private (voluntary) health insurance premiums
3. public (compulsory) health insurance premiums (or tax)

$$WTP_{direct\_oop} \leq WTP_{private\_ins} \leq WTP_{public\_tax}$$

¬ But – can we expect this additive relationship[1] to be (always) true?

[1]cf. D. Gyrd-Hansen (2013)

Economic Literature: Preferences for Health

Are (Many) Stated Preference Studies Misspecified?

- Restricted to individual "use value" (health state, duration, probability)?
- Comparators and cost attribute included?
- "Given that CV studies in health care are overwhelmingly constructed to elicit use-value alone, the question that arises therefore is whether CV studies in health are misspecified.
- Empirical research suggests that […] most CV studies in health care may indeed be misspecified, as a significant element of the value of the good in question is not being captured (Smith, 2007)."[1]

[1]cf. R.D. Smith, T.C. Sach, *Health Economics, Policy and Law* 2010; 5: 91-111

Economic Literature: Preferences for Health

Contingent Valuation (CV) of Health[1]

- Smith and Sach identified 265 CV Studies (published from 1985 – 2005):
  - Focus on **Use Value** of Health only, 73%
  - Focus also on **Option Value**, 13%
  - Focus also on **Externalities**, 5%
  - Focus including **Option Value and Externalities**, 9%
- Arguably, **Option Value** and **Externalities** will be most important when access to high technology and/or costly interventions is at stake – *i.e., in practice, when most*
- **Health Technology Assessment**s *are conducted*

[1]cf. R.D. Smith, T.C. Sach, *Health Economics, Policy and Law* 2010; 5: 91-111

Perspectives on the Social Value of Health Care

A Broad Range of Empirical Preferences

indicating expectations 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.

[1]see, for example, M. Schlander, S. Garattini, S. Holm, et al., *Journal of Comparative Effectives Research* 2014; 3 (4): 399-422.

A Rapidly Growing Economic Literature

on a Broad Range of Characteristics[1]
contributing to **Social Value Judgments**

- Attributes of the Health Condition
  - individual valuation of health conditions
  - severity of the condition
  - unmet medical need
  - urgency of an intervention
  - capacity to benefit from an intervention
- Attributes of the Persons Afflicted
  - non-discrimination (and claims-based approaches)
  - age (and fair innings)
  - other patient attributes
  - fairness objectives; aversion against *all-or-nothing* decisions

[1]see, for example, M. Schlander, S. Garattini, S. Holm, et al., *Journal of Comparative Effectives Research* 2014; 3 (4): 399-422.

A Rapidly Growing Economic Literature

Stated Preference Studies

reporting public preferences for health care priority setting[1]

- Health Care Delivery
  - health benefits
    (type of, i.e., prevention, size of benefit, harm reduction, cause of harm…)
  - non-health benefits (often valued to a lesser extent)
- Patient Groups
  - prioritize by health gain (length and/or quality of life)
  - severity of illness (before and after treatment)
  - (younger) age and socioeconomic status
  - caregiver status, lifestyle / responsibilty
  - availability of effective alternatives
  - cost or cost effectiveness of treatment
  - disease prevalence, equality, waiting times

[1]cf. J. Whitty, E. Lanscar, K. Rixon, et al., *Patient* 2014; 7: 365-386.

A Rapidly Growing Economic Literature

"Understanding What Matters"

Insights from an Australian Focus Group Study including a Ranking Exercise[1]

1. Size of health gain
2. Effectiveness
3. Improvement in quality of life
4. Prevention
5. Cost
6. Cure
7. Number of people
8. Severity
9. Socioeconomic status
10. Indigenous

[…]

[1]cf. J. Ratcliffe, E. Lanscar, R. Walkner, Y. Gu, *Health Policy* 2017; 121: 653-662.

Social Preferences: Research Need

- **Limitations of the literature**
  - many studies limited in size and / or scope
  - many studies likely to be impaired by framing effects
  - sometimes questionable methodology (not choice-based)
  - zero sum assumption in many studies
  - *ex ante* severity probably best documented attribute
    – but distinct difficulties to quantify impact
  - role of prevalence ("rarity") controversial
- **Cost attribute** (payment vehicle in most studies)
  - typically reflecting an individual (selfish) health state valuation (or "out-of-pocket" willingness-to-pay) perspective
  - *whereas citizens' social willingness-to-pay for coverage of health care programs under a collectively financed health scheme would appear more relevant*

Social Preferences: Research Need

What About "Rarity"?

a. **Norway:**
   Arna S. Desser et al. (2010)

b. **Norway:**
   Arna S. Desser (2013)

c. **United Kingdom** (England, Scotland and Wales):
   Warren G. Linley and Dyfrig A. Hughes (2013)

d. **Canada:**
   Emmanouil Mentzakis et al. (2011)

e. **Canada:**
   Nick Dragoijlic et al. (2015)

Some Acronyms

- **URD**
  - Ultra-Rare Disorders
- **ESPM**
  - European Social Preference Measurement Project
- **SoPHI**
  - Societal Preferences for Health Care Interventions Study

How to Evaluate Interventions for URDs?

URD Project 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 (DKFZ & U of Heidelberg / Germany)[1]
- Steven Simoens (U of Leuven / Belgium)
- Oriol de Sola-Morales (IISPV, Barcelona / Spain)
- Harry Telser (Polynomics / Switzerland)[2]
- Keith Tolley (Tolley HE, Buxton / England)
- Mondher Toumi (U Aix-Marseille / France)

[1]ESPM Project & SoPHI Study Leader; [2]Co-Leader of SoPHI Study

How to Evaluate Interventions for URDs?

- **Agreement on Key Challenges (2012)**
- **Agreement on Way Forward (2014)**

JOURNAL OF MARKET ACCESS & HEALTH POLICY

ORIGINAL RESEARCH ARTICLE

Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement

Michael Schlander[1,2,3*], Silvio Garattini[4], Peter Kolominsky-Rabas[5], Erik Nord[6], Ulf Persson[7], Maarten Postma[8,9], Jeff Richardson[10], Steven Simoens[11], Oriol de Solà-Morales[12], Keith Tolley[13] and Mondher Toumi[14]

- specific challenges that arise when applying conventional HTA methodologies to the evaluation of rare and ultra-rare disorders (URDs) / orphan products
- promising ways forward (notably, MCDA and social cost value analysis), overcoming the loopholes of currently prevailing evaluation paradigms
- need for more empirical research into "social preferences" – notably wrt "rarity"
- development of **European Social Preference Measurement (ESPM)** project

How to Evaluate Interventions for URDs?

- Expert Workshop in Berlin / Germany,
  [ISPOR] November 08, 2012
- Expert Workshop in Dublin / Ireland,
  [ISPOR] November 07, 2013
- Expert Workshop in Amsterdam / The Netherlands,
  [ISPOR] November 13, 2014
- Expert Workshop at Heidelberg Health Economics Summer School,
  September 16, 2015
- Expert Workshop in Milan / Italy,
  [ISPOR] November 12, 2015[1]
- Expert Workshop in Heidelberg / Germany, September 28, 2016
  in conjunction with Heidelberg Health Economics Summer School 2016,
  formation of Scientific Steering Committee and agreement on study protocol
- SoPHI Study Phase I: Implementation in Switzerland,
  as of January 2017

[1]supported by unrestricted educational grants from BioMarin and Genzyme (2013 - 2016); in 2012, from BioMarin and Alexion

ESPM Project: Research Objectives

1. To investigate how the general public valuates selected characteristics ("attributes") of health care interventions, with special emphasis on the "rarity" attribute,

   and how they weigh them against each other (including their interaction).

2. To compare the valuation results obtained 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.

1.-3.: [Project Phase I: Pilot Study in Switzerland assessing feasibility; followed by European Phase II incorporating lessons learnt]

4. (in Phase II:) 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: "***European Social Preferences Measurement***" **project**; currently, project phase I (SoPHI study: "*Societal Preferences for Health Care Interventions*" in Switzerland is undergoing final evaluations, after completion of qualitative and quantitative pretests and of main DCE survey during 2017.

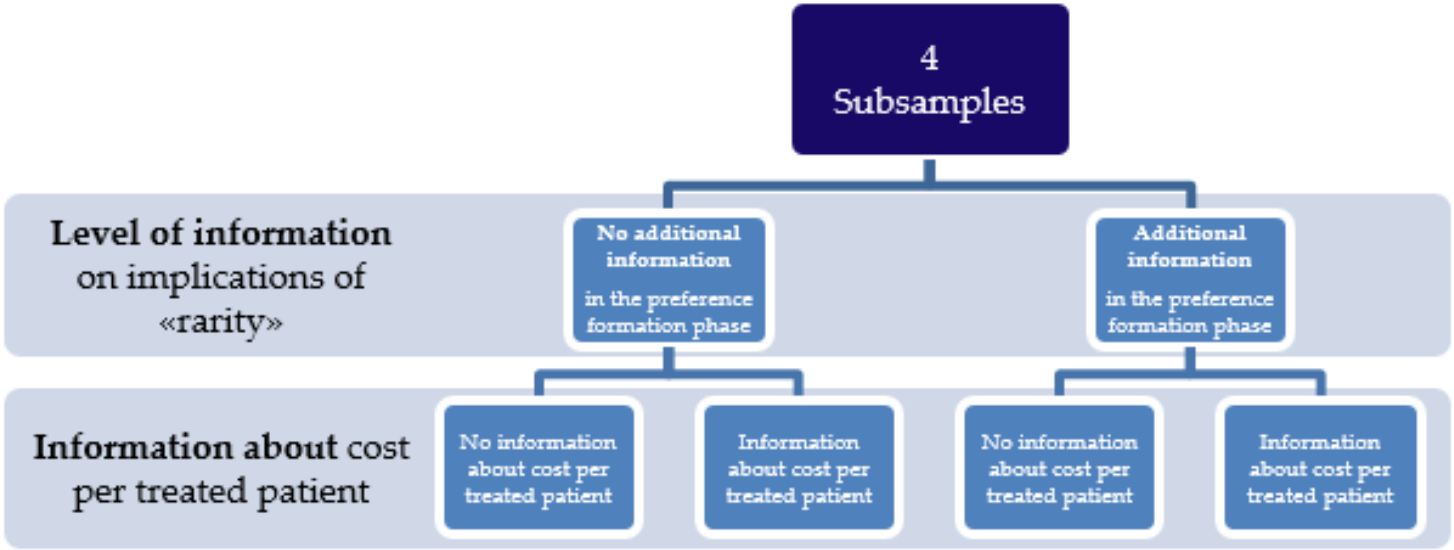
ESPM Project: Design Elements

1. **Representative population sample**
   - 1,501 respondents from Switzerland in Study Phase I
2. **Discrete Choice Experiment (DCE) design**
3. **Initial Preference Formation Phase**
   - prior to DCE experiment
4. **Testing for framing effects** (by randomization):
   - different levels of information on implications of rarity
   - information on cost per patient (either provided or withheld)
5. **Perspective on costs**:
   - incremental compulsory health insurance premiums
6. **Utility comparator** (with generic health state descriptions)
7. **Econometric evaluation**
   - incl. testing for interaction of attributes; subsamples, latent class, and random coefficient models

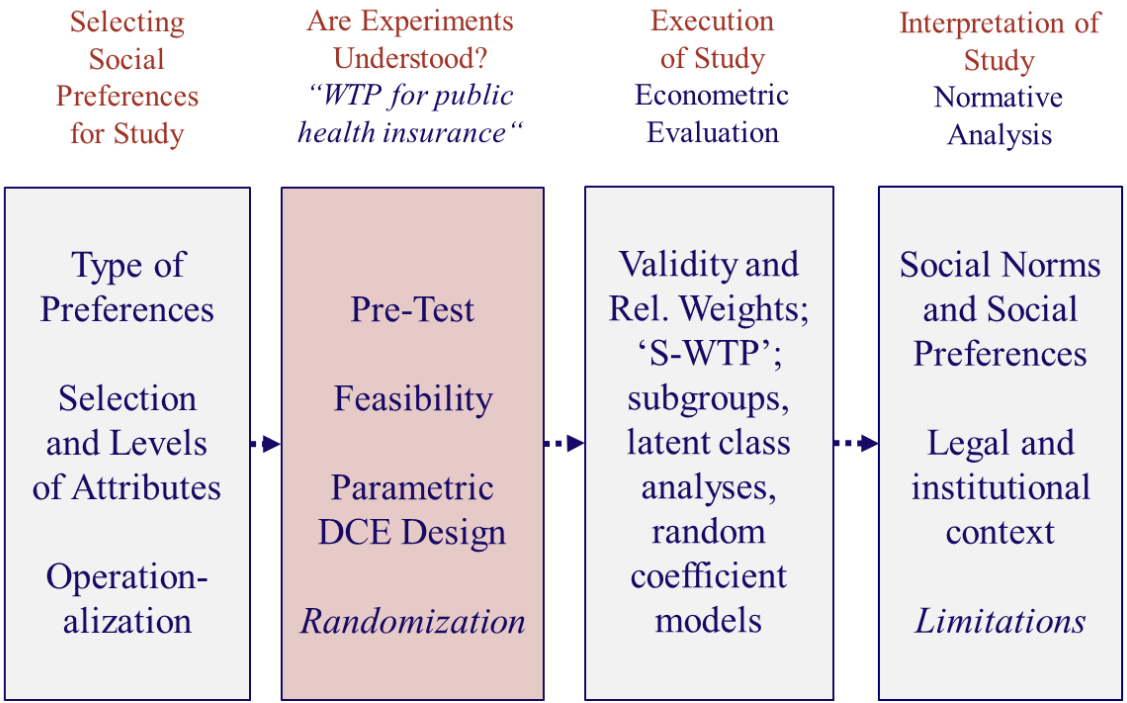
ESPM Project: Design Elements

Testing for framing effects (by randomization):

- different levels of information on implications of rarity
- information on cost per patient (either provided or withheld)



ESPM: Major Steps in Study Phases I and II



ESPM Project: Attributes Investigated

1. **Severity** of the initial health state: lost life expectancy (i.e., *ex ante*, before / without an intervention)
2. **Severity** of the initial health state: lost quality of life (i.e., *ex ante*, before / without an intervention)
3. **Effectiveness** of an intervention: life expectancy gained
4. **Effectiveness** of an intervention: quality of life gained
5. **Age** of patients (or "fair innings")
6. **Rarity** of disorder (i.e., prevalence or number of persons benefitting)
7. **Cost** of intervention: perspective of a compulsory health scheme ("OKP"); payment vehicle = social willingness-to-pay

SoPHI Study: Attributes Investigated

Attribute	Status Quo	With (new) Treatment
Age of Patients	mainly children, on average 10 years old mainly young adults, on average 40 years old mainly elderly, on average 70 years old	
Prevalence	1 in 20, i.e. about 400,000 persons in Switzerland 1 in 200, i.e. about 40,000 persons in Switzerland 1 in 2,000, i.e. about 4,000 persons in Switzerland 1 in 50,000, i.e. about 160 persons in Switzerland	
Health State	very good good good fair / impaired fair / impaired fair / impaired low / severely impaired low / severely impaired low / severely impaired low / severely impaired	very good very good good very good good fair / impaired very good good fair / impaired low / severely impaired
Life Expectancy (depending on age of patients)	45 (10), 60 (40), 75 (70) 45 (10), 60 (40), 75 (70) 45 (10), 60 (40), 75 (70)	52 (10), 64 (40), 76 (70) 66 (10), 72 (40), 78 (70) 80 (10), 80 (40), 80 (70)
Cost	no extra cost	60 CHF per year (= 5 CHF per month) 120 CHF per year (= 10 CHF per month) 360 CHF per year (= 30 CHF per month) 600 CHF per year (= 50 CHF per month)

SoPHI Study: DCE

Decision Cards

Example Decision 1 of 11	Standard Treatment	New Treatment
Who is affected by the disease?	mostly adults, on average 40 years old	
How many people are affected by the disease?	1 of 200, i.e. about 40'000 persons in Switzerland	
Quality of life of patients	moderate	good
Life expectancy of patients	60 years	72 years
How much is your **health insurance premium** increasing?	No increase	120 CHF per year (= 10 CHF per month)

No ☐ Yes ☐

click on the info button to see the description of the attribute

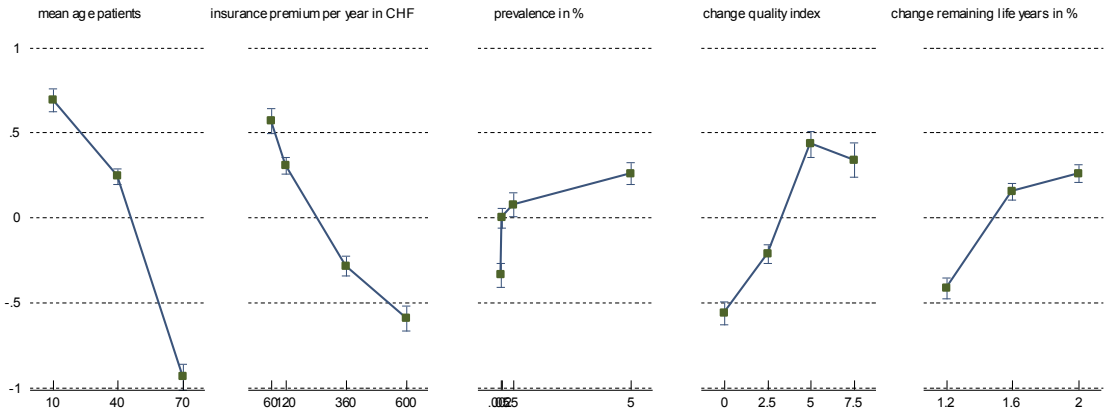
Example Decision 1 of 11	Standard Treatment	New Treatment
Who is affected by the disease?	mostly adults, on average 40 years old	
How many people are affected by the disease?	1 of 200, i.e. about 40'000 persons in Switzerland	
Quality of life of patients	moderate	good
Life expectancy of patients	60 years	72 years
Additional **treatment costs** per patient and year	no additional treatment costs	20'000 CHF per patient and year
How much is your **health insurance premium** increasing?	No increase	Your premium is increasing by 120 CHF per year (= 10 CHF per month)

No ☐ Yes ☐

click on the info button to see the description of the attribute

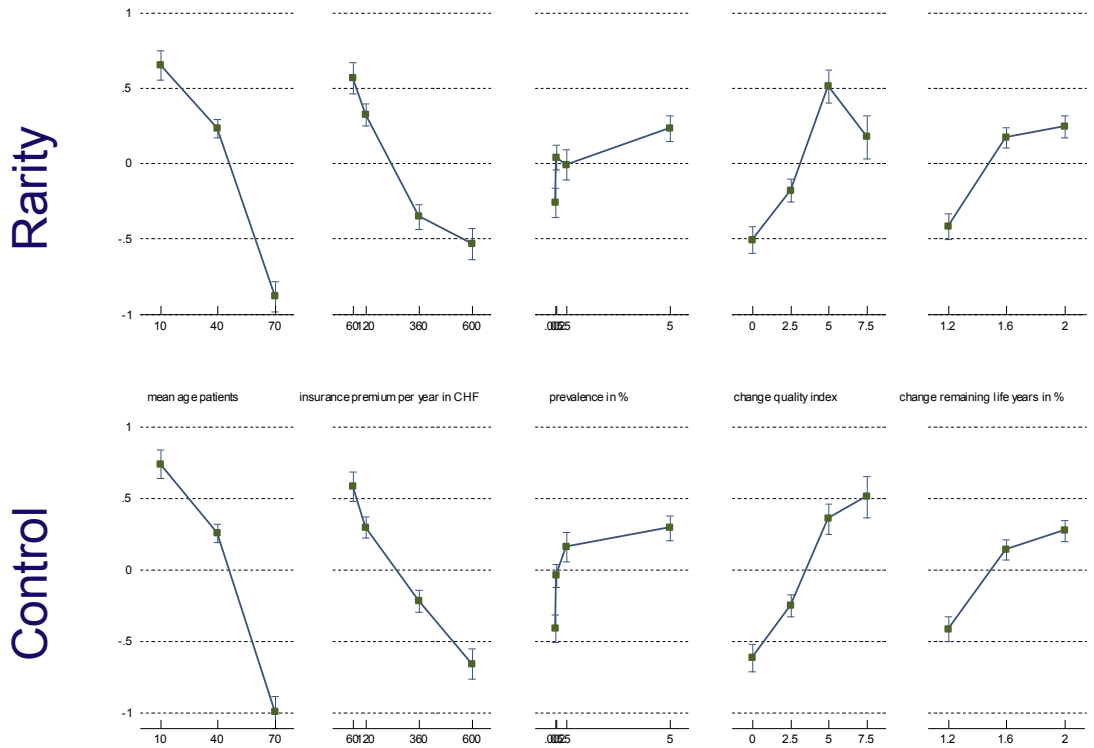
SoPHI Study: DCE Results

Flexible Specification with Dummy Variables

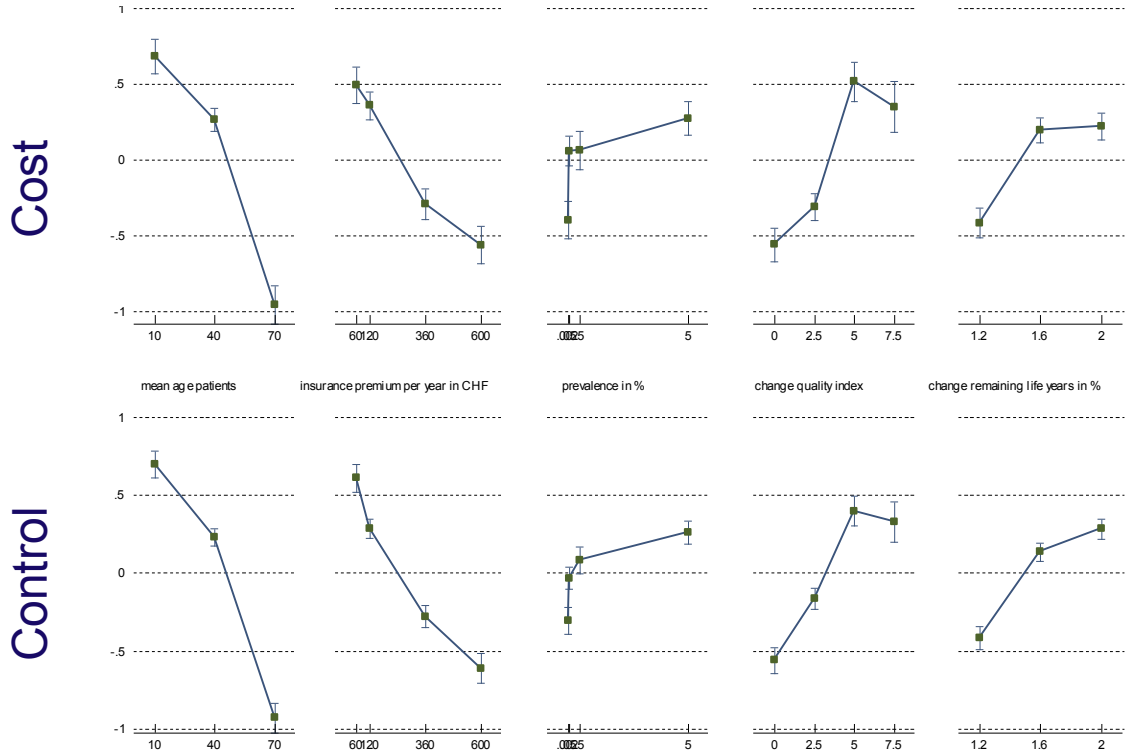


All characteristics are specified as indicator variables
(without requirements for functional form)

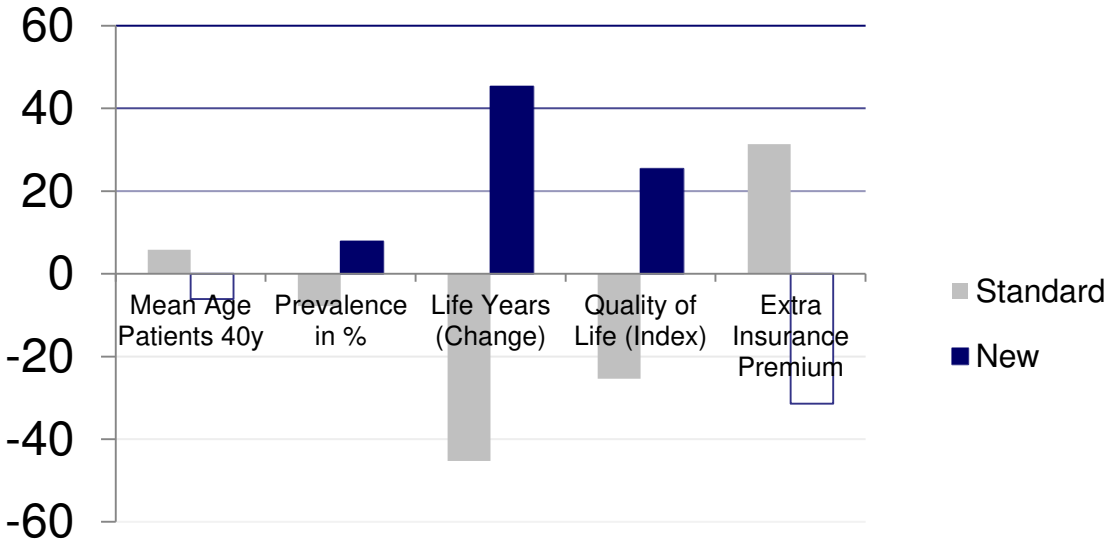
Control for Framing Effects (1): "Rarity"



Control for Framing Effects (2): "Cost / Patient"



Marginal Effects of Attributes



Marginal effects on ***probability of choice*** [dp/dx in % points] of the variables after minmax rescaling at variable means

SoPHI Study: Results

Importance of Attributes

The marginal effect of each variable depends on the overall utility level and is not constant.

The variables with the highest impact on choice probability were

- change in remaining life years
- quality of life (indexed)
- extra insurance premium per year

The negative marginal effect for older people was three times larger compared to middle-aged people. The impact of prevalence was comparable to the age effect.

Subgroup analyses

by level of reflection on implications of "rarity" in initial PFP:

Both groups showed a decreasing valuation of an intervention with decreasing prevalence of the disorder. This effect was much larger than the decrease of prevalence, and by implication the **accepted cost per patient increased with rarity**. Providing additional information on implied cost per patient – had little impact on valuation only.

SoPHI Study: Next Steps *(ongoing)*

- *Social Willingness-to-Pay* Analysis
- Assessment of implied *WTP per case*
- Assessment of implied *WTP per LYG*
- Comparison with *Cost Utility Analysis*
- Assessing *Preference Heterogeneity*
- Finalizing Full Study *Reports*
- Discussing potential *Policy Implications*
- Identifying *Research Needs for Phase II*
- Search for ***Funding*** for Study Phase II

From CUA to MCDA and SCVA

SCVA: Social Cost Value Analysis

- **Social WTP**
  capturing the will to share health care resources[1]
  (option value and externalities)

Potential attributes influencing the will to share may include[1]

- **severity** of the initial health state
- certain **patient attributes**
- a strong dislike for "**all-or-nothing**" resource allocation decisions
- **rights**-based considerations

[1]cf. J. Richardson et al. (2012; 2017); see also E. Nord (2017), and many further sources, discussed – for example – in Schlander et al. (2014)

SCVA: How Different is it from CUA?

Moving from CUA to SCVA would be of little consequence, if and when

- the QALY calculation algorithm offered an adequate proxy for individual [health-related] utility gains,
  - including the transformation of length and quality of life inherent in the QALY model and further assumptions,
- individual [health-related] utility gains mapped into social [health-related] utility gains,
- citizens were not risk averse,
- citizens had little (if any) consideration for others,
  - which would eliminate any non-selfish preferences (for sharing health care resources),
- citizens' WTP was proportional to the number of patients benefitting from the adoption of a health care program.

SCVA: A Changing Perspective

shifting the focus
from cost per patient to cost at program level

- A **decision-makers**' (and payers') perspective
  has been traditionally overall **budgetary impact** (*transfer cost*)

- A **social value** perspective

  (instead of a narrow focus on QALYs as a proxy for individual health-related "utility" and their aggregation) corresponds to social **opportunity cost** (or [social] value foregone) being reflected by net budgetary impact (*transfer cost*)

- This reflects the type of decisions informed by HTAs,
  i.e., decisions on the adoption of health technologies
  at the level of programs (*not* at the level of individual patients)

Thank You for Your Attention!

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