Cost-effectiveness analysis alongside clinical trials

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Heidelberg, October 15, 2019

Overview

- **Introduction**
  - Division of Health Economics
  - Economics and Health Economics
- **Health Technology Assessment**
- **Conventional cost-effectiveness analysis**
- **Data requirements**
  - Resource utilization and costing
  - Health outcomes
- **Sources of evidence**
- **Challenges in real-world application**

Division of Health Economics

- **The Division of Health Economics was established in 2017**

- **The Division aims to contribute to**
  - the advancement of applied health economics;
  - our understanding of the economics of cancer care;
  - improvements of the effectiveness and efficiency of medical care for cancer patients.

- **The Division and its work is**
  - strictly science driven;
  - policy-relevant;
  - politically aware, without acting as a political player.

Division of Health Economics

- **The approach of the Division can be characterized**
  - as multidisciplinary and inclusive;
  - by plurality of thought and method;
  - by openness and transparency,

  including the value judgements underlying its work.

- **The Division´s modus operandi will consistently include**
  - a culture of mutual support and mentoring of young scientists;
  - ethical conduct, including adherence to “best practice” standards;
  - a process of internal quality assurance.

Division of Health Economics

- **Research areas are concentrated within three pillars:**
  - Burden of disease studies
    - Cancer related burden of disease
    - Attributable cost of illness
    - Budget impact of interventions
    - Socioeconomic impact analysis
  - Cost-value analyses of intervention strategies in
    - Cancer prevention
    - Screening
    - Diagnosis
    - Treatment and care
  - Research into the conceptual underpinnings of health economic analyses
    - Health economic evaluation methods
    - Citizens' social norms and preferences

Division of Health Economics

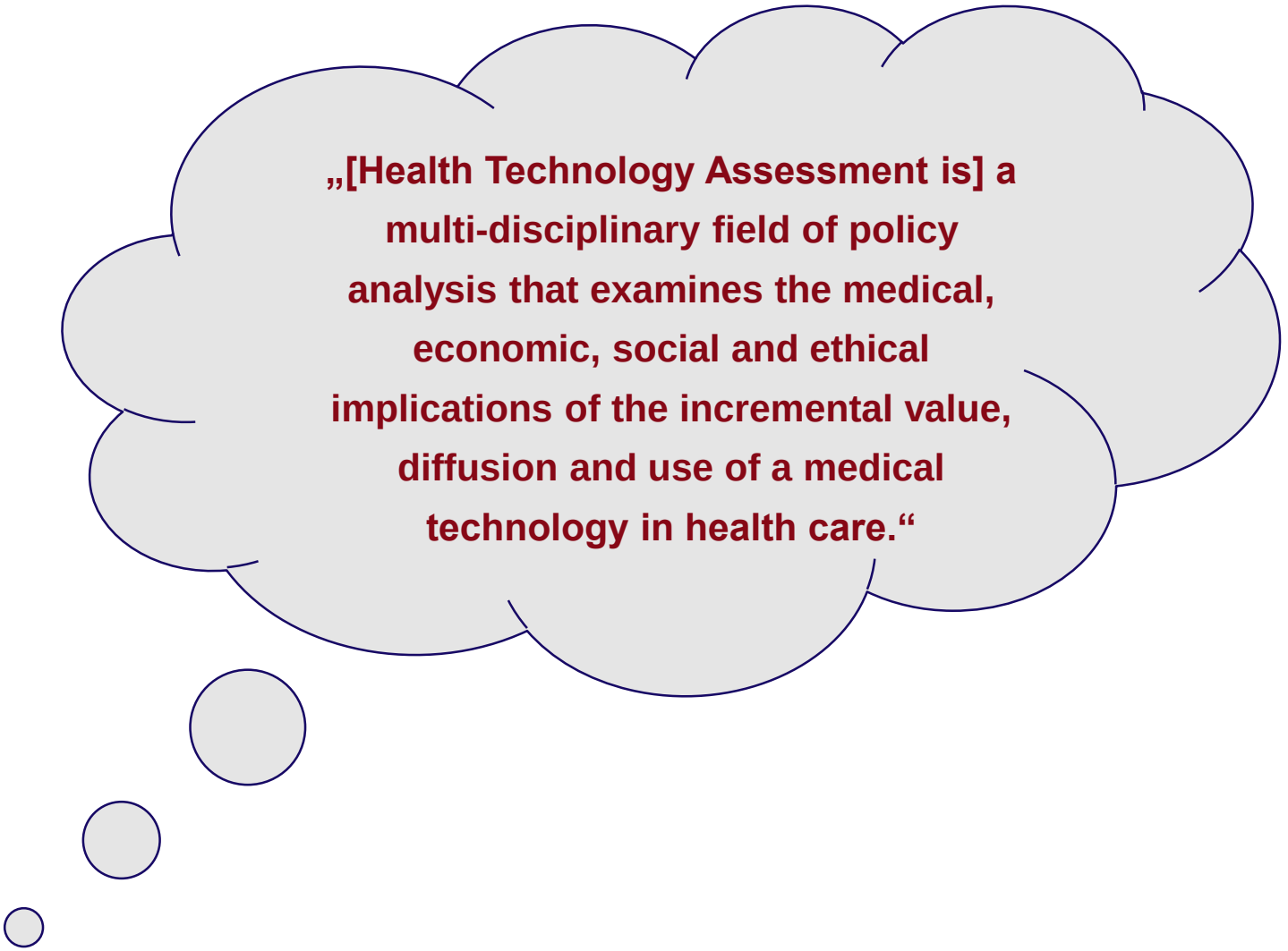
Potential ways of collaboration

- **Applied health economics strives to inform the sphere of policy-making which implies real consequences for health care systems and the provision and reimbursement coverage of services.**

- **Outreach**
  - Education (e.g. Health Economics Summer School)
  - Clinical trial planning (e.g. design of protocol, data collection plan)
  - Cooperation in the evaluation of clinical trial data
  - Conducting health economic evaluations alongside clinical trials
  - Publishing and presenting the results of health economic evaluations
  - Supporting translation of research into clinical practice

Economics and Health Economics

- **Economics may be seen as “science of rational decision making”**
  - Choice between alternative uses of scarce resources
  - Adjusting unlimited needs to limited resources
- **Health economics focuses on allocation of scarce resources related to producing and distributing health care**
  - A multidisciplinary approach analyzing the resource allocation in the health sector (usually within budget constraints)
- **Applied health economics uses**
  - Techniques inherited from economics and decision science
  - Approaches of other disciplines (e.g. mathematics, sociology)
  - Techniques developed specifically for health economic analyses



INATHA (International Network of Agencies for Health Technology Assessment

Health Technology Assessment (HTA)

- **HTA supports decision making on introduction and reimbursement of new health technologies.**
- **Question of HTA: *Is the new technology good value for money?***

- **HTA synthesizes the best available evidence and information on**
  - clinical effectiveness and patient reported outcomes,
  - health-related quality of life,
  - safety,
  - resource utilization and costs

  in order to facilitate informed decision making from various perspectives.

- **A full health economic evaluation requires adequate data from prospective studies to ensure the accuracy of results.**

Health Technology Assessment (HTA)

Typical questions of decision makers

1. Does the new health technology provide health gain (either survival or quality of life or both)?

2. Does the new health technology provide more health gain than the current standard of care?

3. Does the new health technology provide more health gain at an acceptable cost?

4. If yes, do we have enough resources to reimburse the new health technology?

Health Technology Assessment (HTA)

Stakeholders

- Patients
- Family members and caregivers
- Health care payers (e.g. insurance funds)
- Health care decision makers
- HTA agencies
- Tax payers
- The society as a whole

Health Technology Assessment (HTA)

When to conduct HTA?

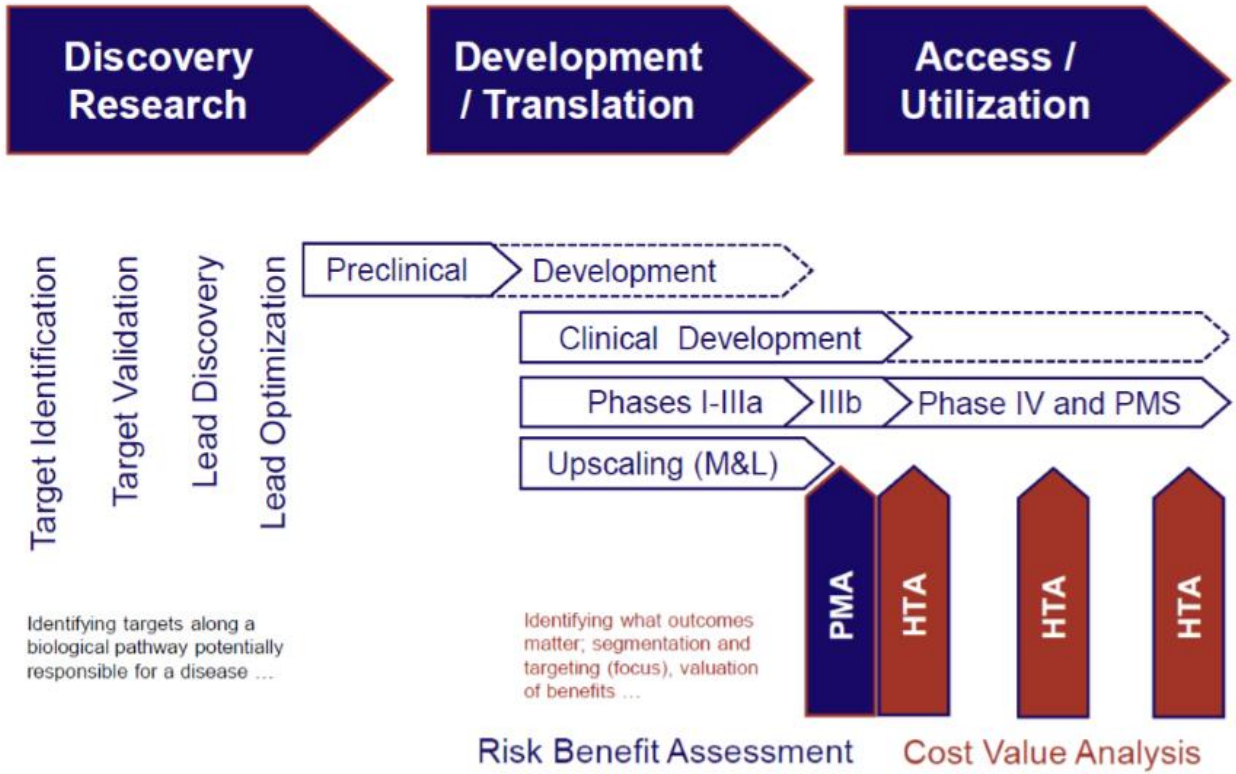


Figure 1. When to conduct HTA?

Source: Division of Health Economics DKFZ.

Health Technology Assessment (HTA)

What kind of health technologies can be assessed?

- Pharmaceuticals
- Medical aids
- Hospital technologies
- Diagnostics
- Screenings
- Public health programs
- Hospital investment
- etc.

Health economic modelling

What is a health economic model?

- **A health economic model is a simplified representation of a real-world phenomenon that aims to help answer one specific decision question.**
  - Not one single method but a process which combines techniques and approaches of economics, mathematics and programming
  - Provides a framework for decisions rather than providing simple yes/no answers

- **Models are supposed to manage complexity of real world**
  - Trade off between accuracy and complexity

Health economic modelling

Why do we need models?

- Clinical trials are often not designed for CEA
- Uncertainty around the parameters
- Lack of data on specific parameters
- Information is available from different sources
- Various decision contexts
- Testing a number of possible scenarios

Health economic modelling

The role of decision analytic models

- **Modelling approaches can support**
  - Structuring the health economic research question
  - Synthesizing evidence
  - Extrapolating beyond observed data
  - Connecting intermediate and final endpoints
  - Generalizing findings for various settings or patient groups
  - Assessing and demonstrating uncertainty around the results
  - Indicating the need for value of further research

Positive and normative health economics

Cost analysis

- **Burden of disease (BoD)**
  - Duration and quality of life loss due to a disorder
- **Cost of illness (CoI)**
  - Total cost (direct / indirect / others) to society due to a disorder
- **Budget impact analysis (BIA)**
  - Predicted impact of adopting a technology on a health care budget (payers´ perspective)
- **Socioeconomic impact analysis (SIA)**
  - Impact of a disorder on patients and their families

Comparative analysis

- **Cost-benefit analysis (CBA)**
- **Cost-effectiveness analysis (CEA)**
  - Cost-utility analysis (CUA)
  - Cost-consequence analysis (CCA)
- **Cost-minimization analysis (CMA)**
- **Social cost value analysis (SCVA)**

Comparative analysis of alternative interventions

Types of cost-effectiveness analyses

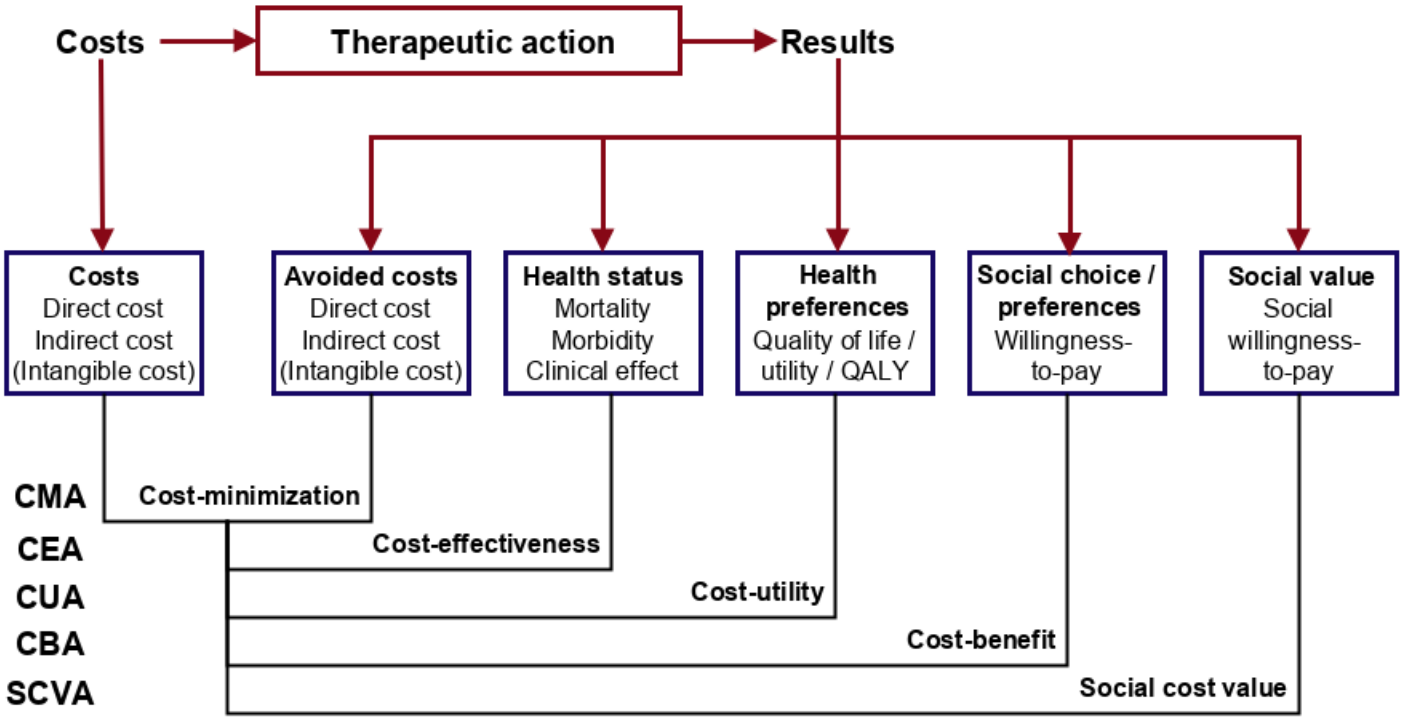
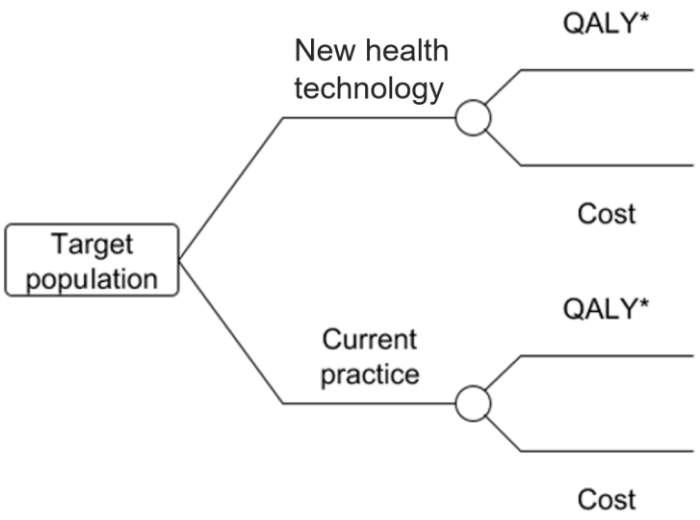


Figure 2. Types of cost-effectiveness analyses

Source: Division of Health Economics DKFZ.

Conventional cost-effectiveness analysis (CEA)#

Model outcomes



* Quality-adjusted life year

Incremental cost-effectiveness ratio:

$$ICER = \frac{Cost_{current} - Cost_{new}}{QALY_{current} - QALY_{new}} = \frac{\Delta Cost}{\Delta QALY}$$

Figure 3. Model outcomes

Please note it is a simplified representation of conventional cost-effectiveness analyses.

Source: Division of Health Economics DKFZ.

Conventional cost-effectiveness analysis

Quality-adjusted life year (QALY)

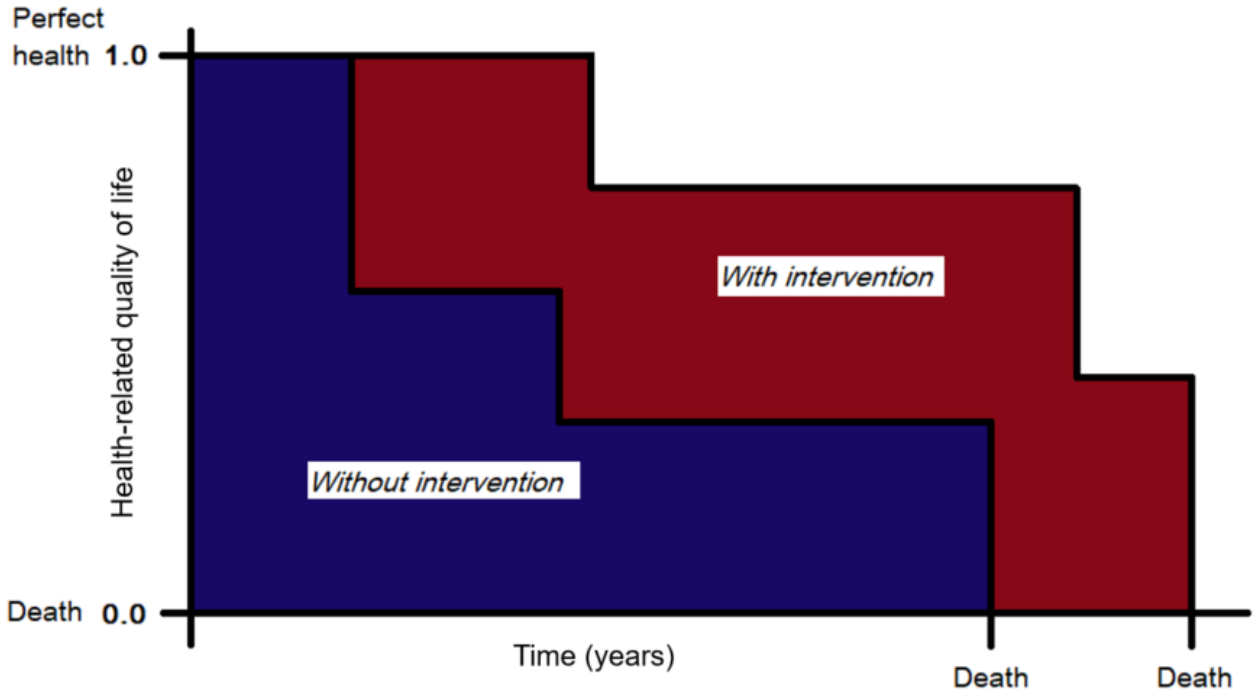


Figure 4. QALY

Source: Division of Health Economics DKFZ.

Conventional cost-effectiveness analysis

Incremental cost-effectiveness ratio (ICER)

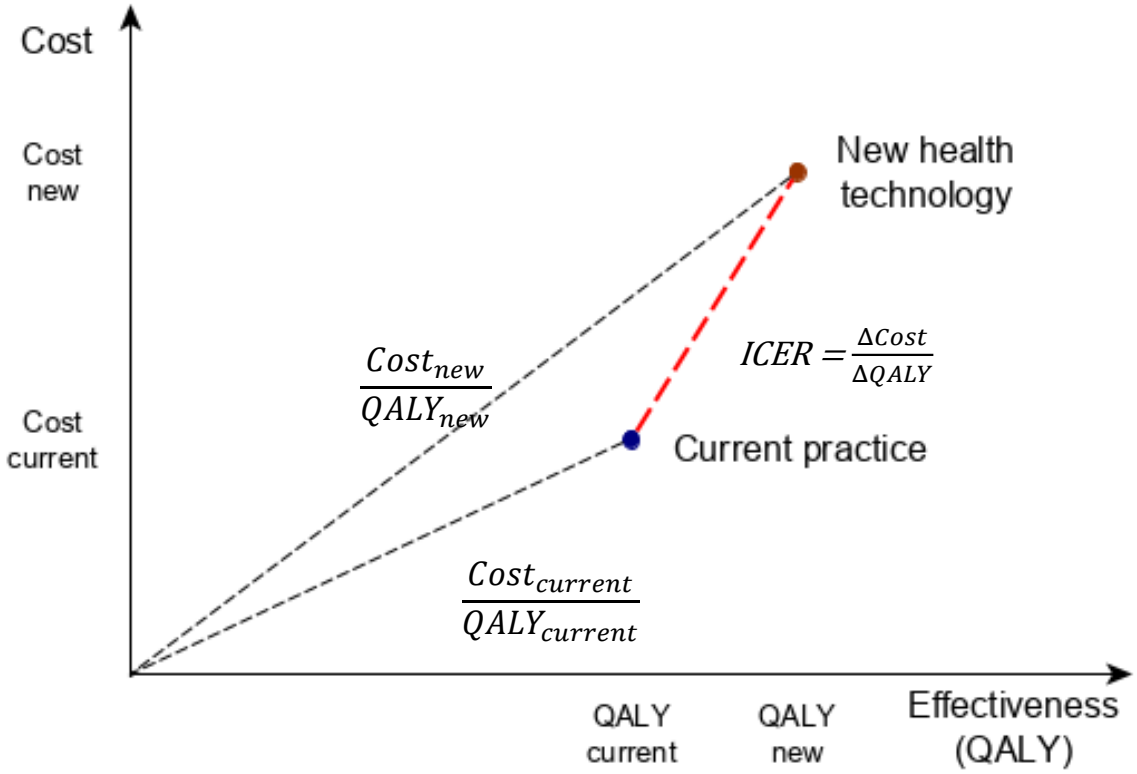


Figure 5. ICER

Source: Division of Health Economics DKFZ.

Conventional cost-effectiveness analysis

Incremental cost-effectiveness ratio

- **Cost-effectiveness analyses are comparative analyses**
  - Cost and health outcomes of the current standard of care (comparator)

  vs
  - Expected cost and health outcomes of the new health technology
- **A medical intervention is never cost-effective itself but only**

  … in relation to a defined alternative (i.e. comparator)

  … in a defined indication

  … for a specific patient group

  … from a specific perspective

  … on a defined time horizon

Conventional cost-effectiveness analysis

Cost-effectiveness plane

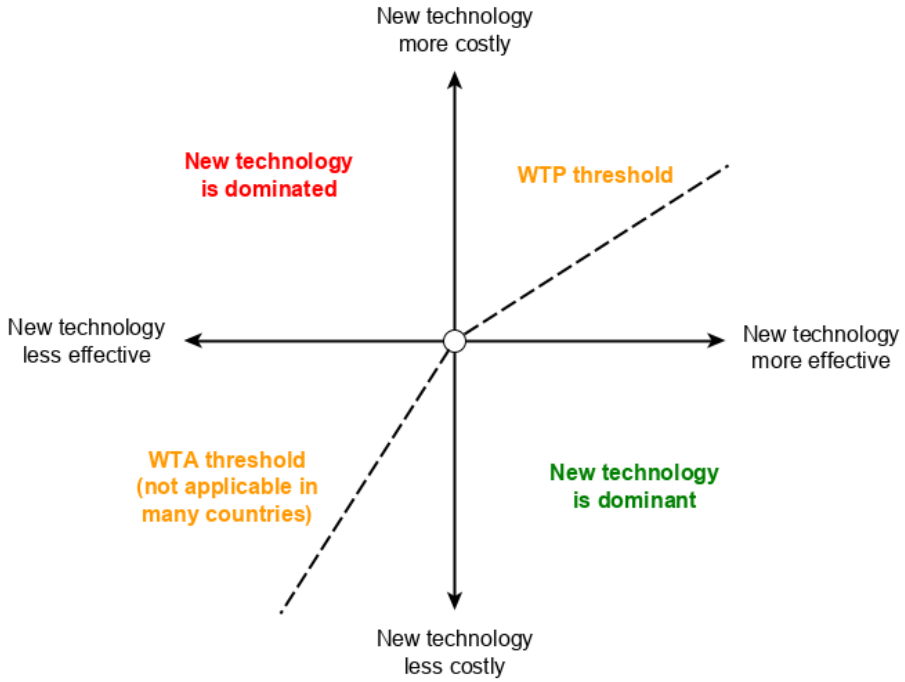


Figure 6. Cost-effectiveness plane

Source: Division of Health Economics DKFZ.

WTP threshold:

In case the new technology is more effective and more costly, the maximum amount of money we are willing to pay for the gain of one QALY.

WTA threshold:

In case the new technology is less effective and less costly, the minimum amount of money we are willing to accept for the loss of one QALY.

Conventional cost-effectiveness analysis

Uncertainty around the outcomes – Outcome of a simulation model

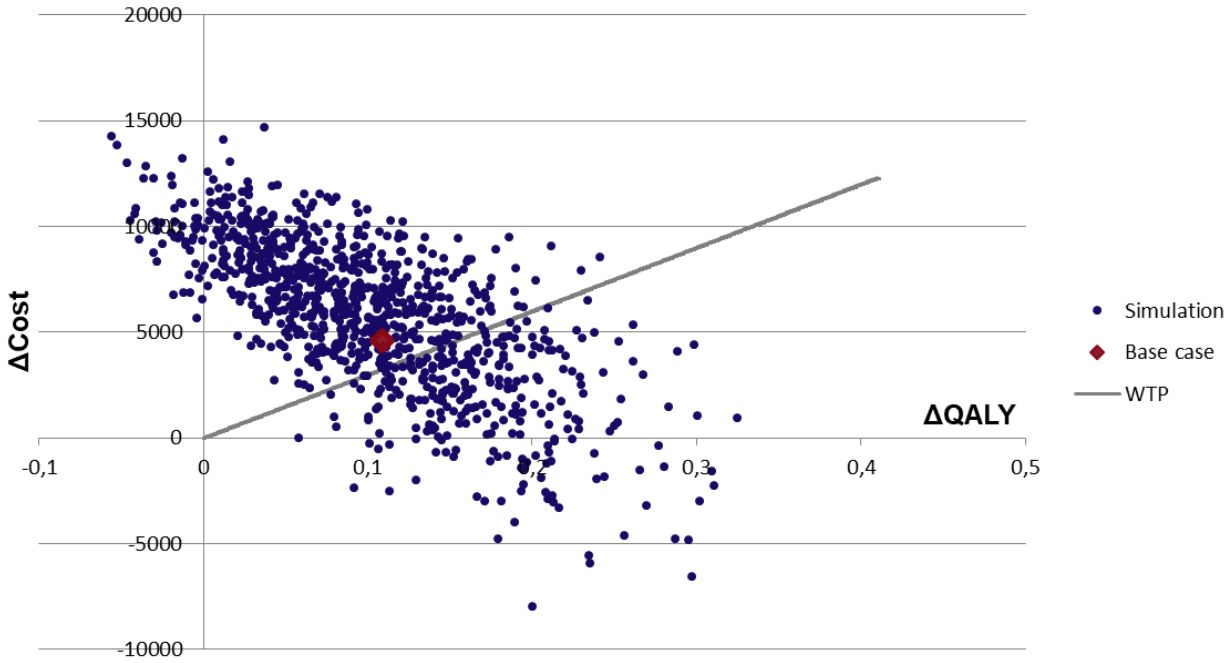


Figure 7. Uncertainty

Source: Division of Health Economics DKFZ.

Conventional cost-effectiveness analysis

Cost-effectiveness acceptability curve (CEAC)

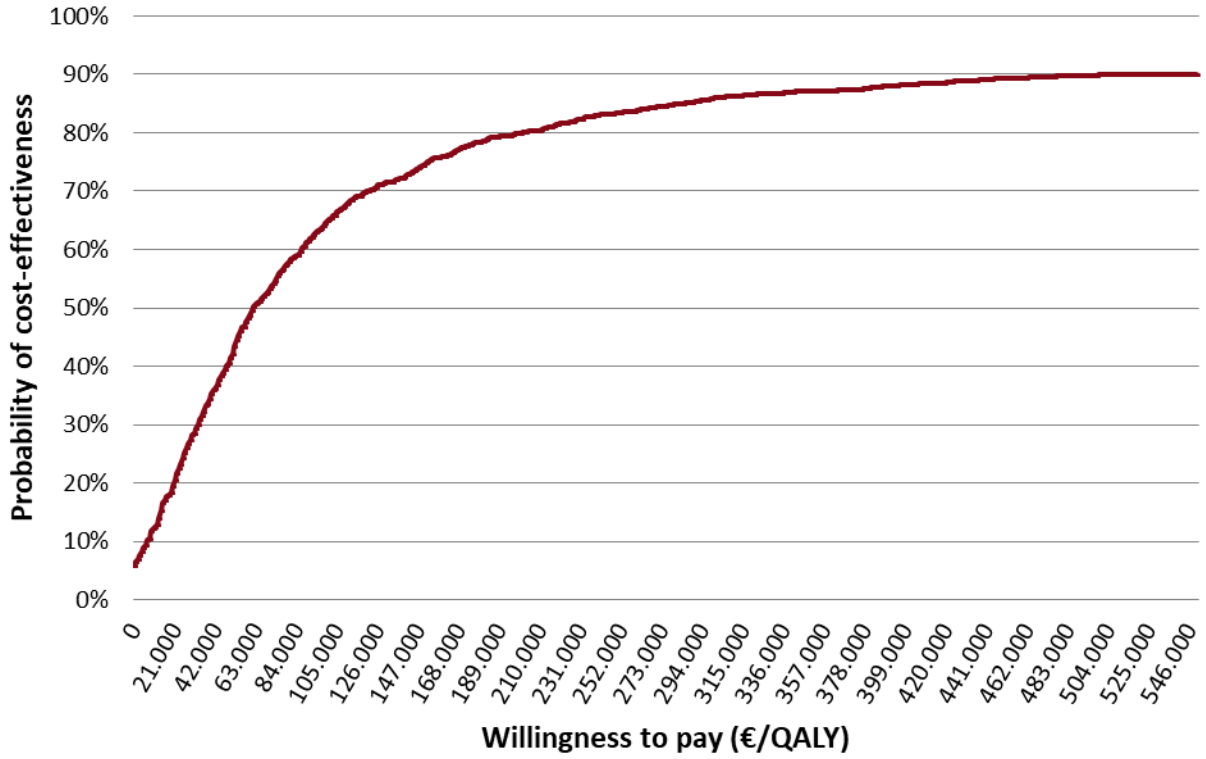


Figure 8. CEAC

Source: Division of Health Economics DKFZ.

Conventional cost-effectiveness analysis

What to expect?

- **Factors affecting health outcomes (examples)**
  - Positive impact:
    - Life years gained (e.g. increased survival due to treatment)
    - Better quality of life (e.g. treatment targeting pain)
  - Negative impact:
    - Worse quality of life (e.g. aggressive chemotherapy during treatment period)
    - Side effects
- **Factors affecting costs (examples)**
  - Positive impact:
    - Avoided interventions (e.g. treatment reduces hospitalization)
  - Negative impact:
    - Induced interventions (e.g. screening programmes)
    - Long-term care

Conventional cost-effectiveness analysis

Marginal analysis

- **Intensity margin**
  - Usually decreasing cost-effectiveness with increasing resource use
  - Examples:
    - Increasing frequency of diagnostic workups
    - Higher dosing of pharmacotherapy
- **Clinical margin**
  - Usually decreasing cost-effectiveness with decreasing severity of the condition
    - Typically addressed by subgroup analyses
  - Examples:
    - Risk-group screening vs. opportunistic screening
    - Therapy option reimbursed only for second line treatment

Conventional cost-effectiveness analysis

Data requirements

- **The quality of the economic evaluation strongly depends on the clinical trial design and data**

- **Health care resource utilization and costs**
  1. Identification (What kind of resources?)
  2. Measurement (How many units?)
  3. Valuation (How much?)

- **Health outcomes**
  1. Clinical outcomes (e.g. overall survival, time to event, cases reported, life-year gain)
  2. Generic outcomes (e.g. QALYs, DALYs)

Costs

What is meant by costs? Opportunity cost

- **Instead of accounting cost, what matters in economics is opportunity cost**

- **Definition:** The **value** of the best alternative

  that is foregone

  in order to produce

  the good under consideration.

Costs

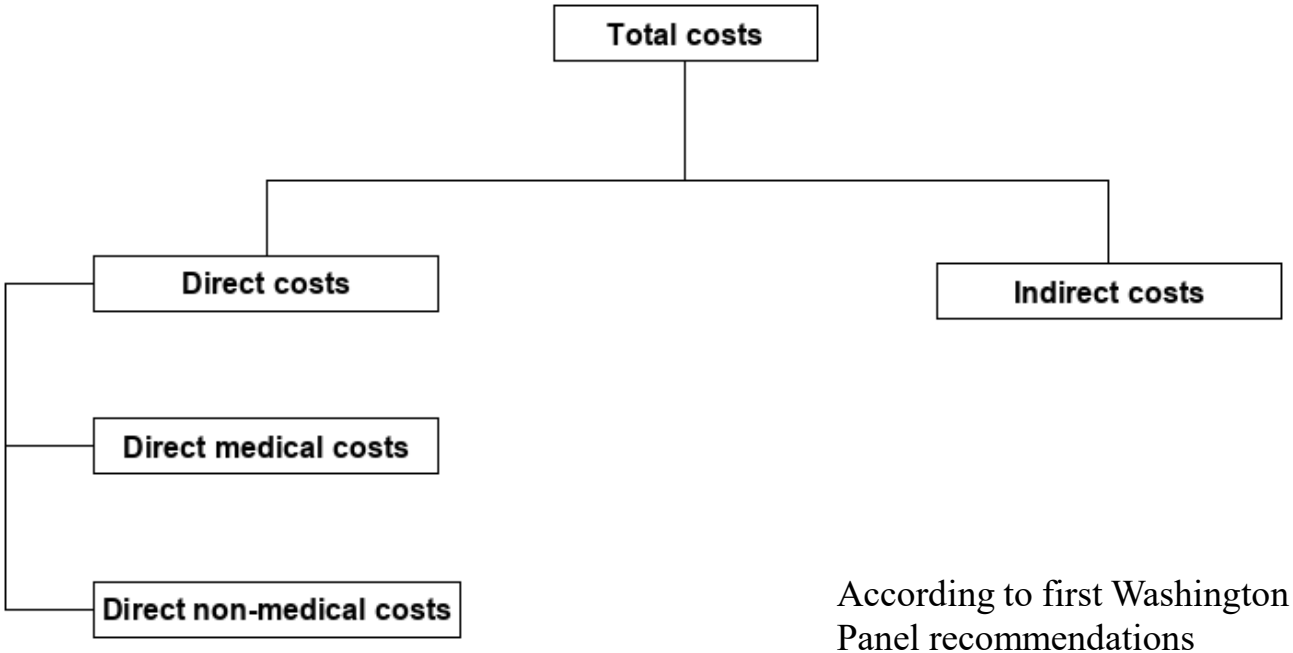
Opportunity cost (cont.)

- **Opportunity cost in other words:**
  - Benefit that could have been received, but was given up, to take another action

- **Examples of opportunity cost:**
  1. Machine to produce one product
     - Earnings from producing other products
  2. A useless machine
     - No opportunity cost
  3. Investment in business
     - Interest rate from savings

Costs

Types of costs in health economic analysis



According to first Washington Panel recommendations

Figure 9. Types of costs

Source: Sanders, Neumann et al, 2016

Costs

Perspective

- **It determines whose costs will be taken into account**
- **Must be defined before the analysis**
- **Major perspectives as recommended by IQWiG in Germany**
  - Societal perspective
  - NHS or [mandatory] health insurance perspective
  - Public service (or social insurance) perspective
  - Employer perspective
  - Individual (patient or family) perspective
  - Citizen (or mandatory health plan member) perspective

Costs

Measurement

- **Cost = Σ(i) [Resources used(i) × unit cost(i)]**
- **Data collection methods:**
  - Accounting documents
  - Case report forms
  - Medical records
  - Questionnaires
  - Patient diaries
- **Choice depends on the research question and resources for research**
- **Resource utilization should be reported separately from cost in economic evaluations**

Health outcomes

Types

- **Clinical outcomes**
  - Usually disease specific measures
  - Not suitable for comparison across various diseases
  - For example: overall survival (OS), progression free survival (PFS), reported events
- **Generic outcomes**
  - Generic composite score combining the length and quality of life
  - Most frequently used generic health outcome: QALY

Health outcomes

Putting the Q into QALYs

- **A key question of valuing health is how to adjust life years to reflect health status experienced during those years**
- **Quality of life (QoL) research and Patient-reported outcome measures (PROMs)**
  - How should quality of life be measured?
  - How should the weights be assigned?
  - How to measure the quality of life impacts on family members and/or caregivers?
- **Health economic analysis requires health-related quality of life (HRQoL) data measured on a cardinal scale**
- **Using utilities:**
  - Health-related quality of life can be measured
  - It is assumed that the range of aspects (domains) of quality of life included allows the resulting QALYs to be comparable across disease areas
  - Broad-based resource allocation decision making

Health outcomes

Different types of QoL instruments

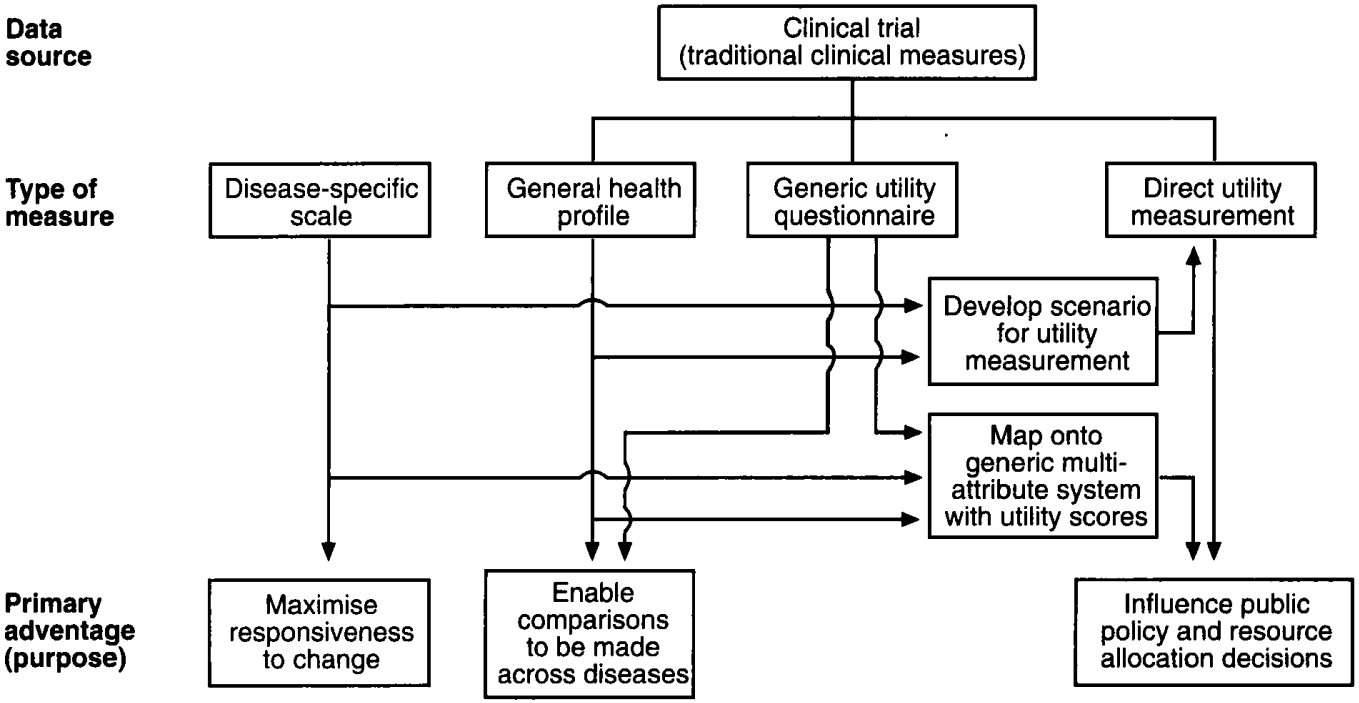


Figure 10. QoL instruments

Source: Drummond MF and Davies LM; Int. J Technol Assess Health Care 1991; 7: 561-73

Health outcomes

Measurement of utilities

- **Direct utility measurement**
  - Individuals directly assess and value specific health states
  - The final utilities reflect to health preferences
  - Most frequently used preference elicitation techniques:
    - Time trade off (TTO)
    - Standard gamble (SG)
  - Other techniques to evaluate health states:
    - Likert scales
    - Visual analogue scale (VAS)

Direct utility measurement

Visual analogue scale (VAS)

- VAS values are not ‘choice based’ and do not conform to the set of axioms which underlie Neumann-Morgenstern utilities, so these are not explicit utilities.

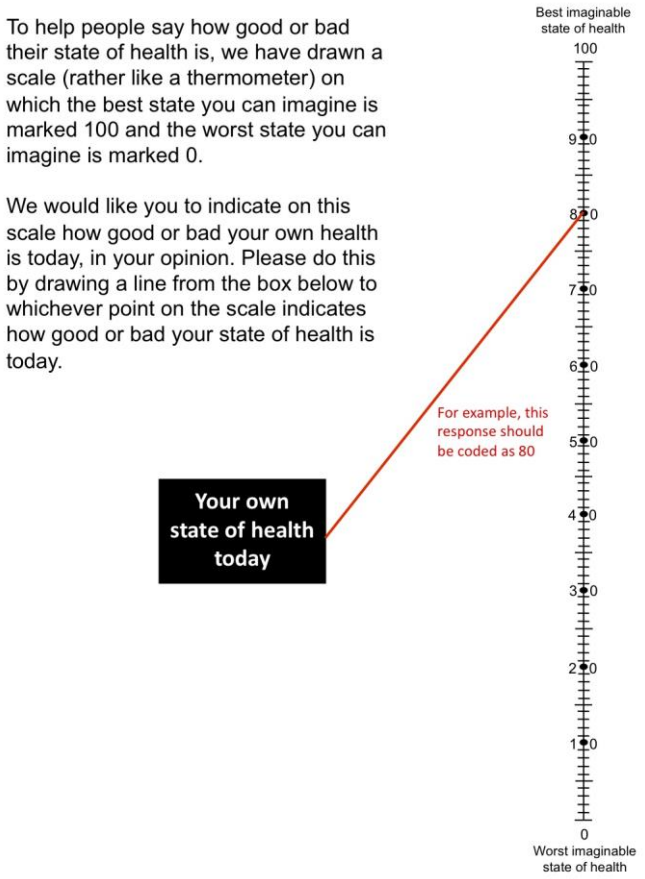


Figure 11. VAS

Source: Office of Health Economics, UK

Direct utility measurement

Time trade off (TTO)

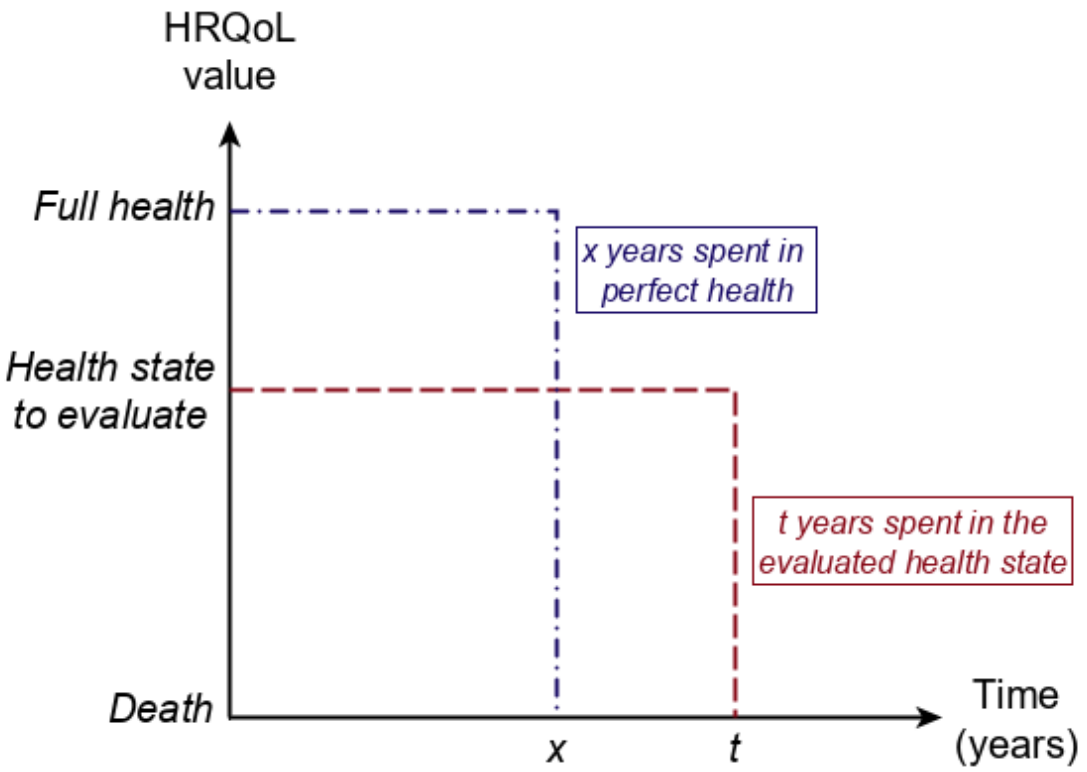


Figure 12. TTO

Source: Division of Health Economics DKFZ.

Direct utility measurement

Standard gamble (SG)

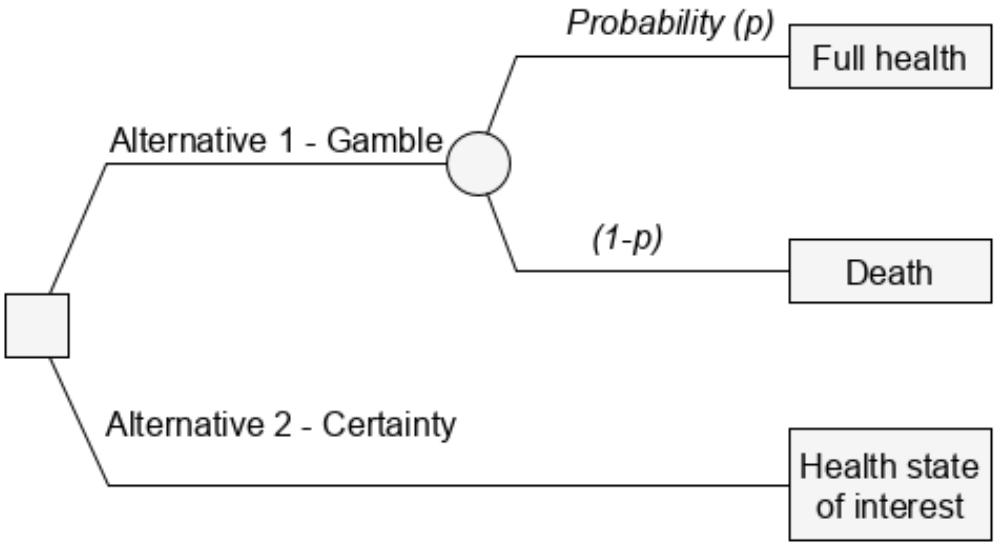


Figure 13. SG

Source: Division of Health Economics DKFZ.

- The probability (p) decreases until the participant is indifferent between Alternative 1 and Alternative 2: *p(ind)*
- Valuation of the health state of interest is equal to *p(ind)*

Health outcomes

Measurement of utilities (cont.)

- **Indirect utility measurement**
  - The patient provides the assessment of his/her health state by health-related quality of life (HRQoL) instruments
  - Many different instruments exist

- **Disease specific instruments example:**
  - EORTC QLQ-C30 for cancer

- **Generic multi-attribute utility instruments (MAUIs) examples:**
  - EQ-5D (Dolan 1997; Shaw et al. 2005)
  - HUI-3 (Torrance 1982; Torrance et al. 1996; Feeny et al. 2002)
  - SF-12 (SF-6D) (Brazier et al. 2002; Brazier and Roberts 2004)

Indirect utility measurement

Generic multi-attribute utility instruments (MAUIs)

- **Various MAUIs have different psychometric properties**
  - Validity
  - Reliability
  - Responsiveness
  - Sensitivity in different diseases
  - Importance of different health dimensions

Generic multi-attribute utility instruments (MAUIs)

Multi Instrument Comparison (MIC) study: Results

Table 1. Pearson correlation between MAU Instruments (total sample, n=1,269)

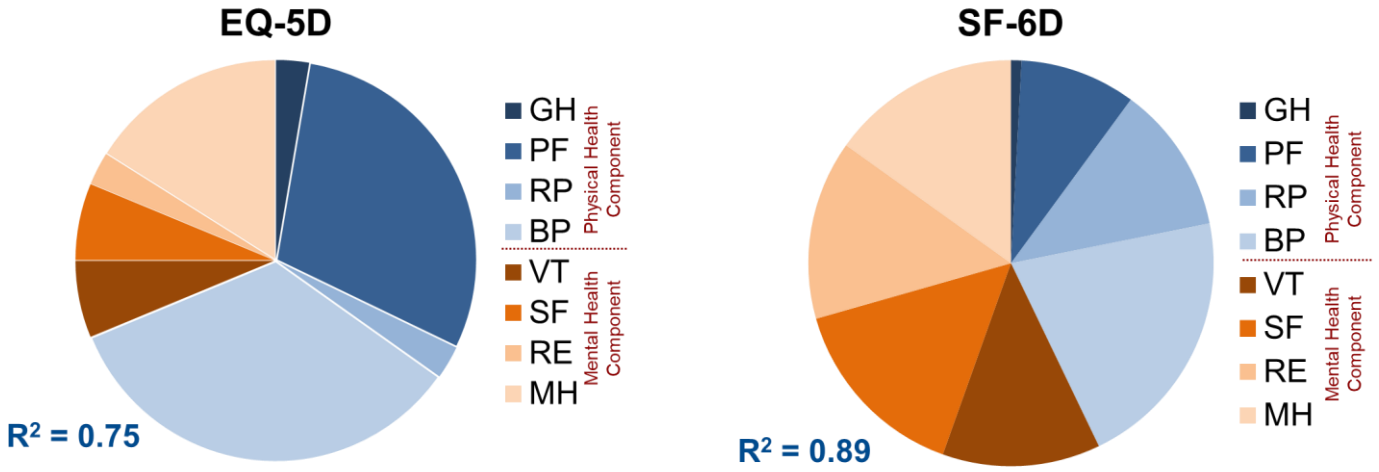
	EQ-5D	HUI3	SF-6D	15D	AQoL-4D	AQoL-8D
EQ-5D	1	.649**	.595**	.654**	.530**	.514**
HUI3	.649**	1	.515**	.649**	.540**	.522**
SF-6D	.595**	.515**	1	.569**	.450**	.648**
15D	.654**	.649**	.569**	1	.558**	.597**
AQoL-4D	.530**	.540**	.450**	.558**	1	.623**
AQoL-8D	.514**	.522**	.648**	.597**	.623**	1
Ave	**0.59**	**0.58**	**0.56**	**0.61**	**0.54**	**0.58**
**. Correlation is significant at the 0.01 level (2-tailed).						

Source: M Schlander et al. The Measurement of Health-Related Quality of Life (HRQoL) - First German Findings from the Multi-Instrument Comparison (MIC) Study. Presentation at the 16th ISPOR Annual European Congress Dublin / Ireland, November 04, 2013

Generic multi-attribute utility instruments (MAUIs)

Multi Instrument Comparison (MIC) study: Results

- **Dissimilarities in the importance of dimensions of different generic instruments (compared to SF-36)**



GH = general health; PF = physical functioning; RP = role limit physical; BP = bodily pain; VT = vitality; SF = social functioning; RE = role limit emotional; MH = mental health

Figure 14. Dissimilarities in the importance of dimensions

Source: M Schlander et al. Differences Across Instruments Measuring Health Related Quality of Life in Germany. Research Poster. 2019

Generic multi-attribute utility instruments (MAUIs)

Multi Instrument Comparison (MIC) study: Some implications

- **The MIC study probably offers the most comprehensive comparison of MAU instruments done in Germany to date.**
- **Differences between MAU instruments**
  - In constructs and descriptive systems
  - Necessarily lead to differences in utility values
- **Particularly large differences between MAU instruments**
  - Related to their psycho-social content
  - May have had a differential impact on health economic evaluations of services by therapeutic area / dimensions of impairment
- **Incremental utilities form the basis of conventional cost-effectiveness analysis but may vary by up to 100 percent between MAU instruments according to geometric regression analyses.**

Source: M Schlander et al. Multi-Attribute Utility (MAU) Instruments as Tools to Value Health-Related Quality of Life (HRQoL). Hamburg. July 16, 2016.

Health outcomes

Factors to consider in QoL measurement

- **Type and sensitivity of the instrument**
  - Disease-specific instruments: sensitive for QoL change but often not able to provide utilities
  - Generic instruments: often not sensitive enough
  - Methodology of deriving utilities
- **Sample size calculations for QoL measurement**
  - Primary clinical endpoint vs secondary endpoint
- **Measuring QoL in multinational studies**
  - Availability of questionnaires in different languages
  - Cultural adaptability
  - Availability of preference weights (per site or country)

Sources of evidence

Quality of evidence and strength of recommendation – The GRADE system

Code	Quality of evidence	Strength of recommendation	Definition
A	High	Strong	Further research is very unlikely to change our confidence in the estimate of effect.
B	Moderate	Conditional (weak)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C	Low		Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
D	Very low		Any estimate of effect is very uncertain.

Source: Division of Health Economics DKFZ. Based on Guyatt et al. (2008) and EBM Levels of Evidence (accessed: 13-09-2019)

Sources of evidence

Levels of evidence and grades of recommendations

GRADE code	Level of evidence	Type of study
A	1a	Systematic review of RCTs
	1b	Individual RCT (with narrow confidence interval)
	1c	All or none RCT
B	2a	Systematic review of cohort studies
	2b	Individual cohort study or low quality RCT (e.g. <80% follow-up)
	2c	"Outcomes" research; ecological study
	3a	Systematic review of case-control studies
	3b	Individual case-control study
C	4	Case-series (and poor quality cohort and case-control studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Source: Adapted from the Centre for Evidence-Based Medicine, Oxford (accessed: 13-09-2019)

How to link clinical data to CEAs (examples)?

Information from clinical trial	Model parameter
¬ Timing of relevant clinical events	¬ Decision on cycle length
¬ Patient characteristics	¬ Subgroup analysis
¬ Clinical effectiveness	¬ Relative treatment effect
¬ Incidence and length of adverse events	¬ Utility decrements
¬ Patient-reported outcomes	¬ Health state utilities (e.g. QALYs)
¬ Surrogate outcomes	¬ Extrapolation (i.e. analysis on longer time horizon)
¬ Resource utilization	¬ Costing

CEAs alongside clinical trials

Challenges

- **Internal validity versus generalizability**
  - Inclusion and exclusion criteria
  - Context of evaluation
  - Population characteristics
  - Different study sites
  - Explanatory rather than a pragmatic trial
- **Choice of comparator treatment**
- **Health outcome measurement**
  - Intermediate vs final health outcomes

CEAs alongside clinical trials

Challenges (cont.)

- **Inadequate length of follow-up (i.e. time horizon)**
- **Protocol-driven costs and outcomes**
  - Blinding effects: same tests and services, regardless of treatment group
  - Patient and physician compliance
  - Screening and therapeutic drug monitoring
  - High case finding due to increased frequency of monitoring
- **Single source analysis vs evidence synthesis**
- **Quality of life measurements**

CEAs alongside clinical trials

Potential solutions

- Relaxing of stringent inclusion/exclusion criteria
- Inclusion of a separate usual care arm in the clinical trial
- Factoring out the protocol driven costs (during analysis)
- Use of open label trial design
- Multicenter studies
- Conducting an observational study parallel to a RCT
- Applying modelling techniques

Conducting health economic evaluations

How to involve the economic analyst?

Phase II

- To ensure that the trial provides necessary data for high-quality health economic evaluation
- Early-phase economic evaluation can be conducted
- Expected value of perfect information (VOPI) studies can be conducted

Phase III

- To ensure an appropriate trial design and the collection of all the necessary data for a high-quality health economic evaluation
- Health technology assessment (HTA) can be conducted

Phase IV

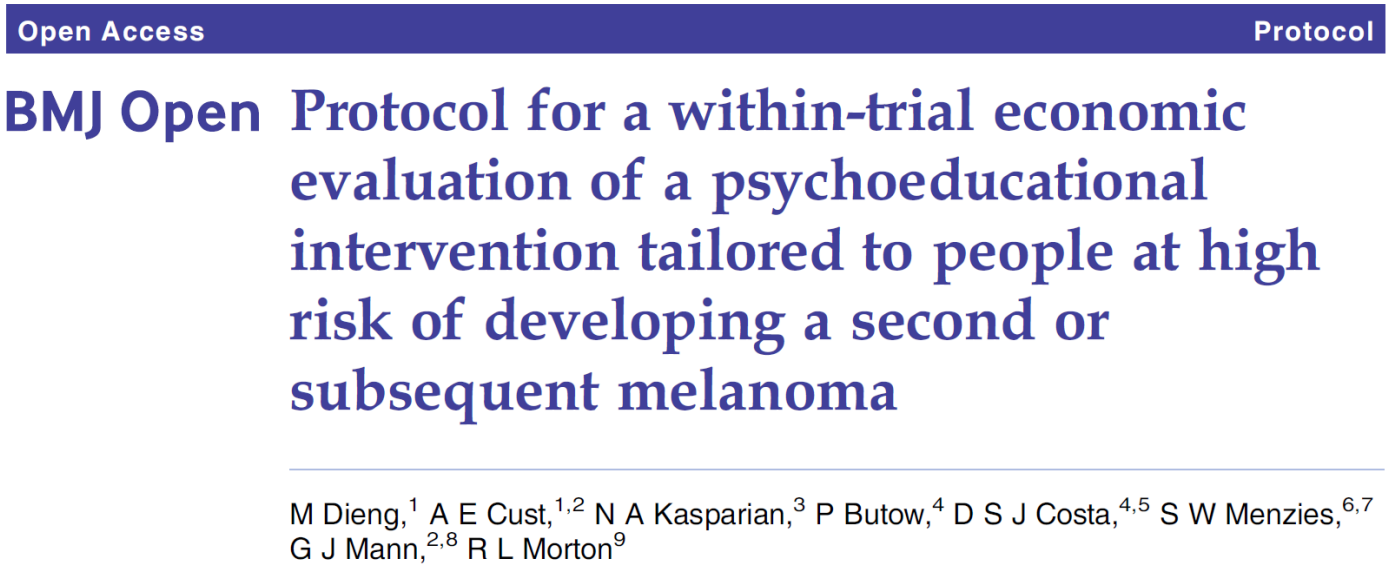
- Monitoring long-term effects for further evidence generation
- Re-evaluation of the new health technology can be conducted

What are the benefits for clinicians and clinician scientists?

- **Increased chance of success with grant applications**
- **Potential translation of research to clinical practice**
  - Reliable cost-effectiveness results
  - Real-world generalizability of clinical outcomes of the study is increased
  - Support for reimbursement
- **Publication output**

An example for CEA alongside clinical trial

New intervention



Open Access Protocol

BMJ Open

Protocol for a within-trial economic evaluation of a psychoeducational intervention tailored to people at high risk of developing a second or subsequent melanoma

M Dieng,[1] A E Cust,[1,2] N A Kasparian,[3] P Butow,[4] D S J Costa,[4,5] S W Menzies,[6,7] G J Mann,[2,8] R L Morton[9]

An example for CEA alongside clinical trial

Motivation

- Research and clinical guidelines support inclusion of psychological and psychoeducational interventions as part of routine clinical care for people with melanoma

- No funded psychological support programmes for melanoma survivors during their post-treatment follow-up

- A major barrier to the implementation of these interventions in routine clinical care is a lack of data on their cost-effectiveness

An example for CEA alongside clinical trial

Methods and analysis

- **Design**
  - Two-arm RCT designed for people with a history of melanoma who are at high risk of developing new primary disease and who were attending one of three high-risk melanoma clinics across New South Wales (NSW), Australia
- **Sample size**
  - Calculated based on the primary clinical endpoints, not the expected difference in cost-effectiveness
  - Relatively limited number of patients attending the high-risk melanoma clinics
  - Cost-effectiveness acceptability curve (CEAC) to demonstrate uncertainty derived from the aforementioned limitation

An example for CEA alongside clinical trial

Methods and analysis (cont.)

- **Patient reported outcomes**
  - Fear of new or recurrent melanoma (severity subscale of a modified, melanoma specific version of the 42-item Fear of Cancer Recurrence Inventory (FCRI) questionnaire)
  - Generic Quality of Life instrument (AQoL-8D preference based measure)
- **Resource utilization and costs**
  - Only costs and effects accumulating for 12 months
  - A combination of administrative records and self reported healthcare utilization (at baseline, at 6 months and 12 months
  - Melanoma related direct costs, hospital and physician visits and allied health service utilization (Psychologists, Dietician, etc)

Thank you for your attention!

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Thank You for Your Attention!

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