



How to interpret pharmacoeconomic studies?

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Conflict of interest statement

**The presenter serves on a
Study Steering Committee for Amgen.
He has no potential or actual conflict of interest with
respect to the contents of this workshop.**

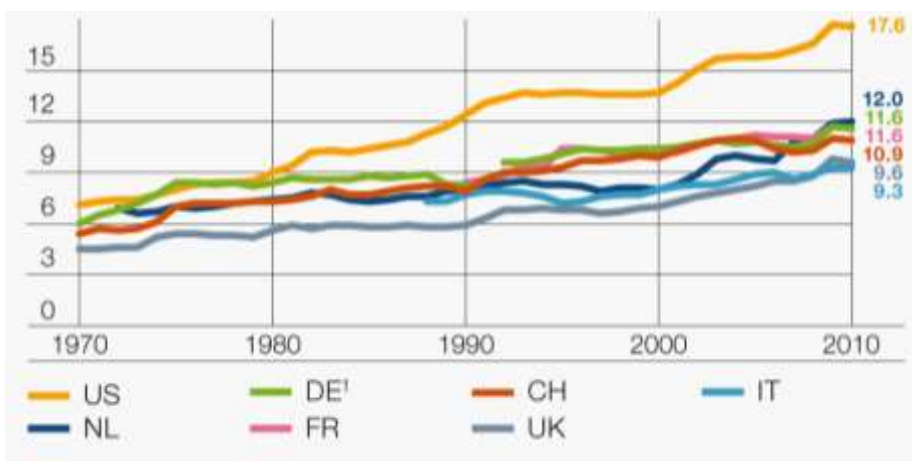
Overview

- Background

- Quality of [reporting of] pharmacoeconomic studies
- Key principles of pharmacoeconomic evaluation
- Use of pharmacoeconomic results in reimbursement decision making

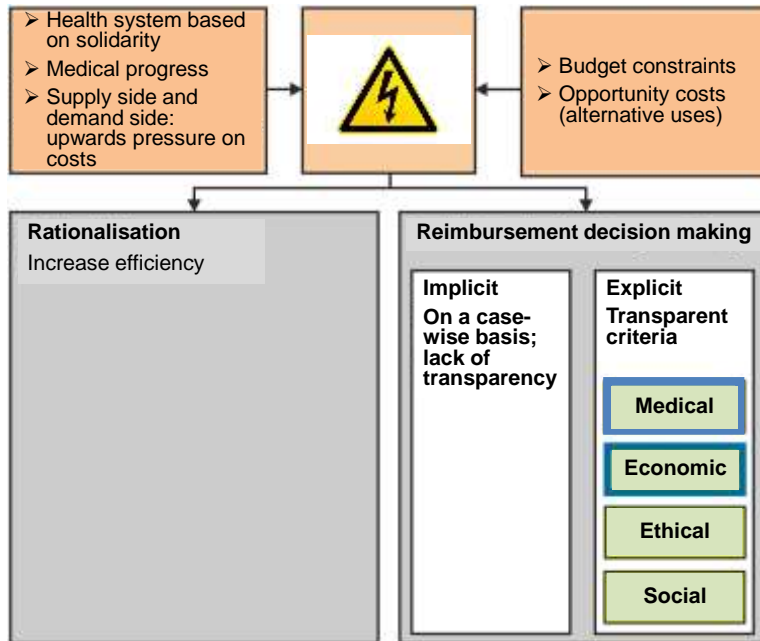
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Health care costs, percent of gross domestic product



Source: OECD Health Data. Paris: OECD 2012. Graph adapted from interpharma

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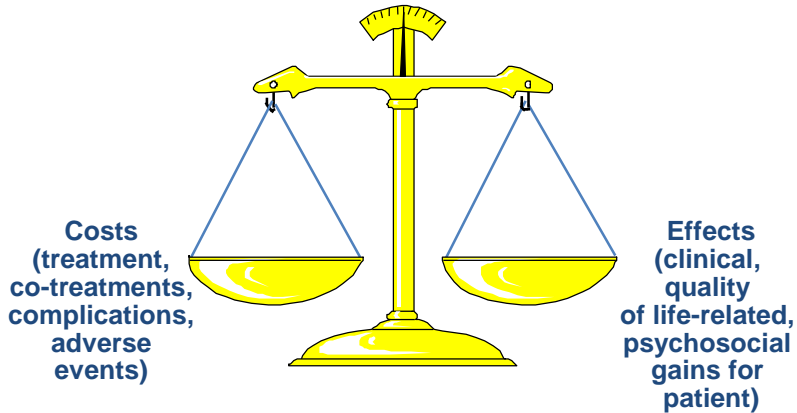


Source: INFRAS in cooperation with M. Schwenkglenks

Pharmacoeconomic evaluation (PEE): integral part of Health Technology Assessment (HTA)

- Clinical efficacy
 - Safety
- Regulatory approval**
-
- Effectiveness under routine practice conditions
 - Costs
 - Cost-benefit relationship (efficiency)
- Core additional elements**
- Equity (egalitarianism)
 - Societal preferences, ethics (e.g. disease severity, unmet medical need), psychological aspects
 - Legal, organisational, professional aspects

Cost-benefit relationship (efficiency)



Is the treatment efficient, i.e. good value for money?

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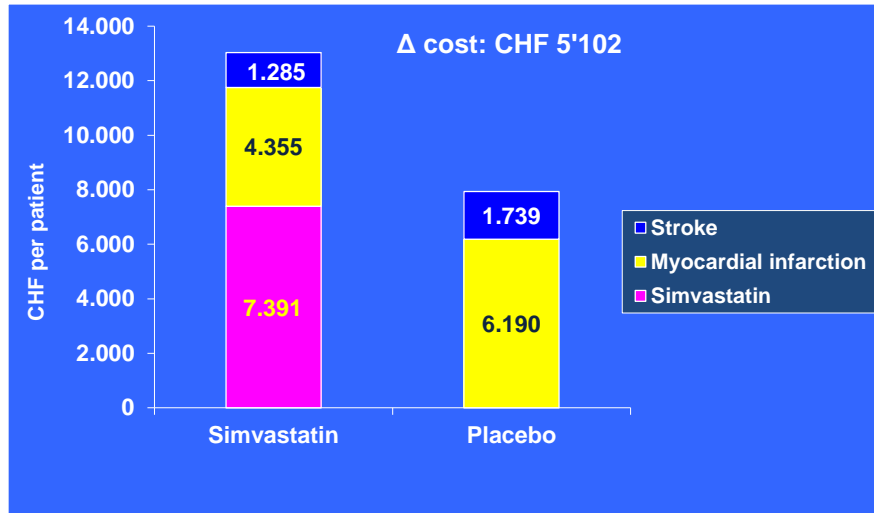
Situations faced by hospital pharmacists: new drug replaces ...

- Drugs used previously, cost-saving for the hospital pharmacy
- Non-drug services performed by the hospital, cost-saving at the hospital level
- Drugs used or services performed in the wider health system, cost-saving at the health system level
- There is an adequate clinical gain but replacement of other drugs or services is limited, no cost-savings



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Historic example: cost of simvastatin in tertiary coronary prevention



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BMJ checklist for economic articles

- Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ*. 1996;313:275-83.
 - <http://www.bmj.com/content/313/7052/275>

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CHEERS checklist for economic articles

- Husereau D, Drummond M et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMC Med* 2013;11:80.
 - <http://www.biomedcentral.com/1741-7015/11/80>
- Husereau D, Drummond M et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) – explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value in Health* 2013;16:231-50.
 - <http://www.ncbi.nlm.nih.gov/pubmed/23538175>

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CHEERS item 4

Target population and subgroups

Describe **characteristics of the base case population** and subgroups analysed, including why they were chosen.

Source: Husereau D, Drummond M et al. BMC Med 2013;11:80

Definition of target population(s)

- Approved label?
- Eligibility criteria of relevant clinical studies?
- Existing guidelines
- Preferences of clinicians?
- Subgroups with improved cost-effectiveness?

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CHEERS item 7

Comparators

Describe the **interventions or strategies being compared** and state why they were chosen.

Which interventions should be compared?

- Intervention of interest and relevant alternative drugs / treatments
- What interventions do we have data for? (For example comparator treatments in randomised clinical trials)
- What do treatment guidelines say?
- What is the established standard of care in the relevant geographies?

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CHEERS item 19

Incremental costs and outcomes

For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, **report incremental cost-effectiveness ratios.**

Source: Husereau D, Drummond M et al. BMC Med 2013;11:80

Independent versus dependent health care interventions

- **Independent health care interventions**
 - Different indications, or combination within a given intervention makes sense
 - Not mutually exclusive
- **Dependent health care interventions**
 - Same indication
 - Mutually exclusive
 - Typical starting point for HEE

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Common characteristics of PEE studies on mutually exclusive health care interventions

- Comparison of two or more medical strategies
- Integration of clinical and economic evidence
- Cost differences between strategies (**incremental costs**) are put in relation to differences in clinical gains (**incremental gains/effects**)

$$\text{ICER} = \Delta \text{ Cost} / \Delta \text{ Effect}$$

ICER, incremental cost-effectiveness ratio

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Use of Guaiac tests (FOBT) to detect colon cancer

No. of tests	Cases identified	Cost (\$) ¹	Average cost (\$) ²
1	65.9469	77'511	1'175
2	71.4424	107'609	1'507
3	71.9003	130'199	1'811
4	71.9385	148'116	2'059
5	71.9417	163'141	2'268
6	71.9420	176'331	2'451

¹ Guaiac tests in 10 '000 patients plus X-ray examination in positive cases

² Total costs divided by true positive cases

Source: Neuhauser D, Lewicki AM. NEJM 1975;293:226

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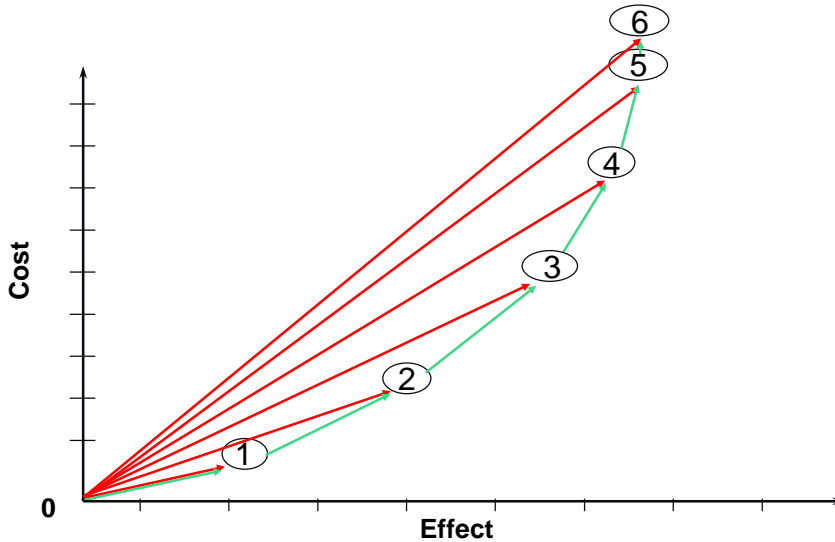
Incremental cases identified and incremental costs

Tests per	Incremental cases	Incremental costs (\$)	Costs per additional case detected (\$)
1	65.9469	77'511	1'175
2	5.4956	30'179	5'492
3	0.4580	22'509	49'150
4	0.0382	17'917	469'534
5	0.0032	15'024	4'724'695
6	0.0003	13'190	47'107'214

Source: Neuhauser D, Lewicki AM. NEJM 1975;293:226

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Average vs. incremental cost-effectiveness



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Cost-effectiveness plane



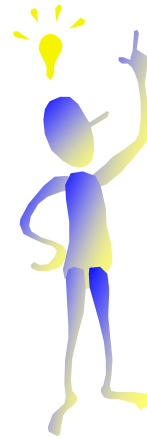
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Pro memoria ...

COST-EFFECTIVE = EFFICIENT

COST-EFFECTIVE ≠ COST-SAVING

COST EFFECTIVE ≠ AFFORDABLE



CHEERS items 1; 10

Title; Choice of health outcomes

Identify the study as an **economic evaluation** or use **more specific terms such as “cost-effectiveness analysis”, ...**

Describe what outcomes were used as the **measure(s) of benefit** in the evaluation and their relevance for the type of analysis performed.

Study types in PEE

- Full scale PEE studies
 - Cost-benefit analysis
 - Cost-effectiveness analysis
 - Cost-utility analysis
- PEE studies in a wider sense
 - Quality of life and utility studies, outcomes research
 - Cost of illness studies
 - Cost-minimisation analysis
 - Budget impact analysis

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Cost-benefit analysis



Cost-effectiveness analysis



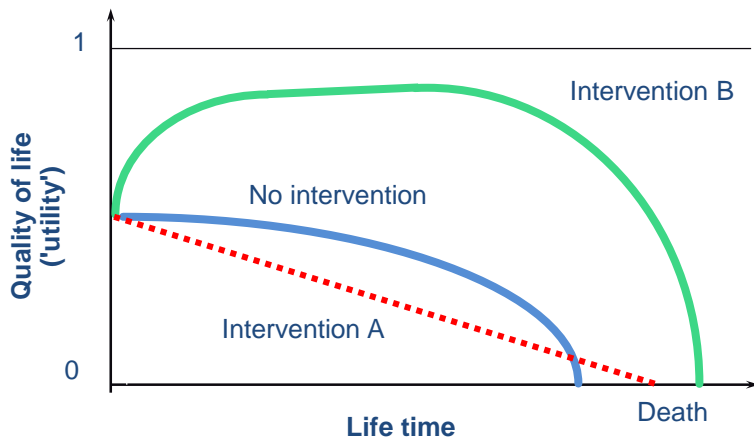
Frequent clinical endpoints in cost-effectiveness analysis

- Lives saved
- Life years saved
- Events avoided (e.g. cardiovascular)
- Cases avoided (e.g. prevention studies)
- Patients who can live independently
- Intermediate clinical parameters (surrogate endpoints, e.g. blood pressure, cholesterol level, bone density)

Cost-utility analysis



Quality-adjusted life years (QALYs)



CHEERS item 11

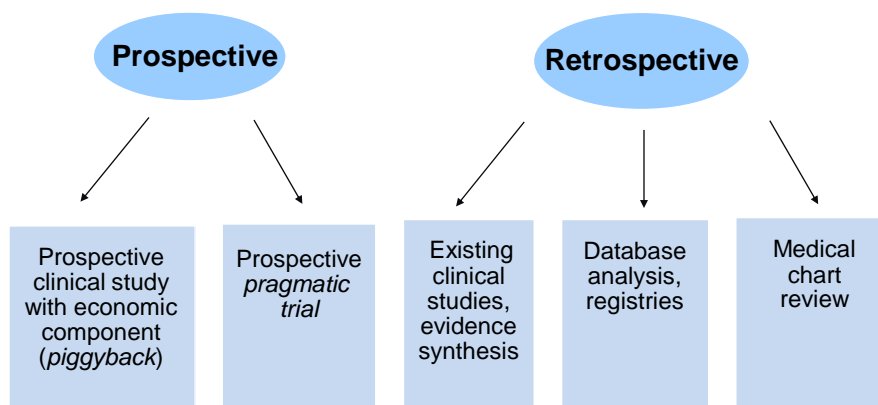
Measurement of effectiveness

11a **Single study-based estimates**: Describe ... design features ... and why the single study was a sufficient source of clinical effectiveness data.

11b **Synthesis-based estimates**: Describe .. methods used for identification of included studies and synthesis of clinical effectiveness data.

Source: Husereau D, Drummond M et al. BMC Med 2013;11:80

Approaches to pharmacoeconomic data collection



In practice, different approaches are typically combined

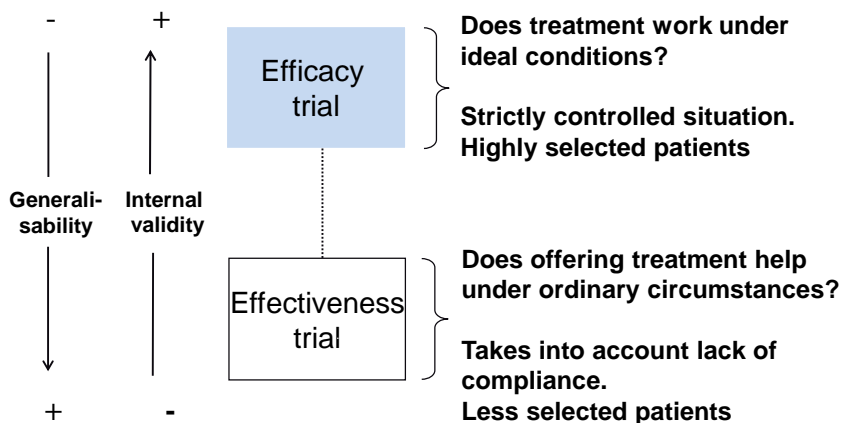
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Data sources for PEE

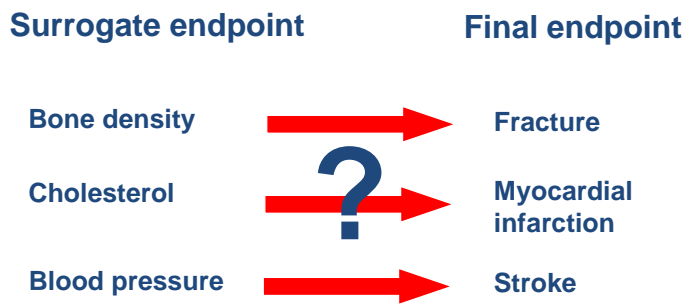
Data type	RCT-based?	Other sources?
Event rates in comparator strategy	Yes	Local registries, epidemiological and clinical databases
Relative risk in active treatment strategy	Yes	Local registries, epidemiological and clinical databases
Long-term survival	If life-expectancy is short	Local registries, epidemiological databases
Utilities	Sometimes available	Published data, separate primary data collection
Medical resource use	Partially	Local resource use studies and registries, health insurance data, expert opinion
(Unit) costs	Bottom-up costing possible	Local cost-of-illness studies, health insurance data, DRG data, national tariff lists, formularies

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Efficacy vs. effectiveness



Types of clinical endpoints



CHEERS item 12

Measurement and valuation of preference based outcomes

If applicable, describe the population and methods used to elicit **preferences for outcomes**.

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Event rates in comparator strategy	Yes	Local registries, epidemiological and clinical databases
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Conventional quality of life instruments

- Generic, e.g. SF-36 (<http://www.sf-36.org/>), SF-12
- Population-specific, e.g. Child Health Questionnaire (<http://www.healthact.com/chq.html>)
- Disease-specific, e.g. EORTC QLQ-C30 in oncology (<http://www.eortc.be/home/qol/ExplQLQ-C30.htm>)
- A database: <http://www.proqolid.org/>

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What is a utility?

- **Measure of preference for a given health state**
- **Used to express self-perceived health-related quality of life on a linear scale from 0 (death) to 1 (perfect health)**
- **Provide a means on incorporating a large number of health, psychological and psychosocial effects**
- **Allow comparing health states across disease states and disease entities**

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Measuring utilities

- **Direct measurement**
 - Visual Analogue Scale
 - Standard gamble (choice in a situation of uncertainty – issue of risk aversion, yields utilities in a narrow sense)
 - Time trade-off (choice in a situation without uncertainty)
- **Indirect measurement**
 - EQ-5D (<http://www.euroqol.org/>)
 - Health Utility Index (Torrance)
 - Quality of Wellbeing Index (Kaplan)
 - Approximation using conventional quality of life data (e.g. SF-36, SF-12)

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Issues regarding utilities/QALYs

- Best way to measure?
- Who is the reference: general population, experts, or patients?
- Reframing of severely diseased patients
- Change over time – how often to measure and when?
- Are QALY-differences driven by survival or quality of life effects; in different populations really equivalent?

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CHEERS items 13; 6

Estimating resources and costs; Study perspective

... Describe approaches used to **estimate resource use** associated with the alternative interventions. Describe primary or secondary research methods for **valuing each resource item in terms of its unit cost**. ...

Describe the **perspective of the study** and relate this to the costs being evaluated.

Source: Husereau D, Drummond M et al. BMC Med 2013;11:80

Data sources for PEE

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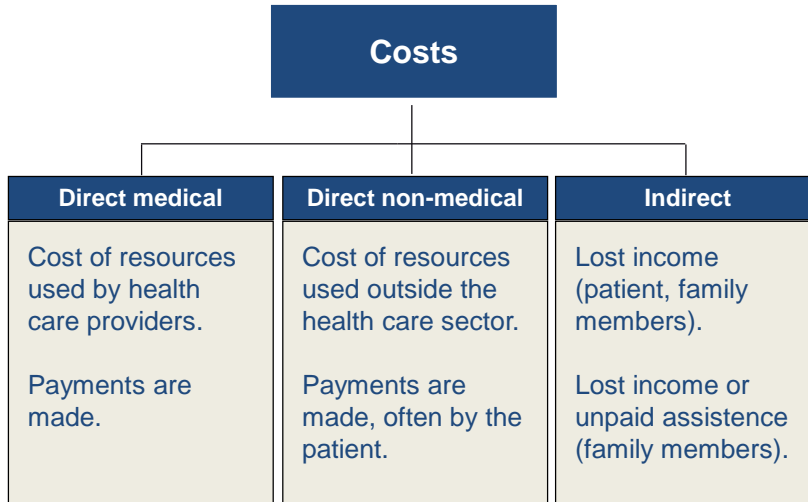
Issues in resource use and cost assessment

- Was a given resource use and cost due to the disease of interest?
- Accessibility and structure of hospital administration/billing data
- Cost-to-charge ratio
- Is it at all helpful to use site-specific resource use and cost data?
- National unit costs may be preferable



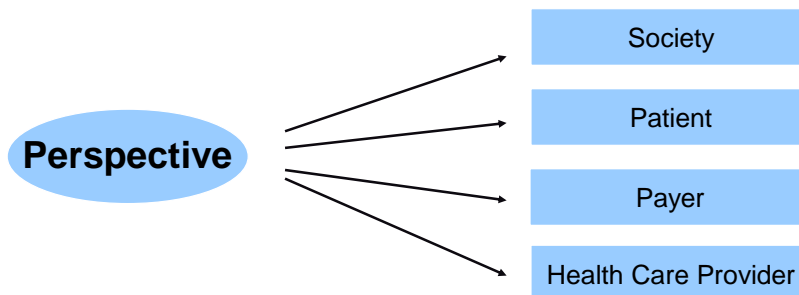
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Types of costs



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Cost assessment: importance of perspective



Perspective defines what to take into account

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CHEERS items 5, 14

Setting and location; Currency, price date, and conversion

State relevant aspects of the **system(s) in which the decision(s)** need(s) to be made.

... Describe methods for adjusting estimated unit costs to the **year of reported costs** if necessary. Describe methods for **converting costs** into a common currency base and the exchange rate.

Source: Husereau D, Drummond M et al. *BMC Med* 2013;11:80

CHEERS item 9

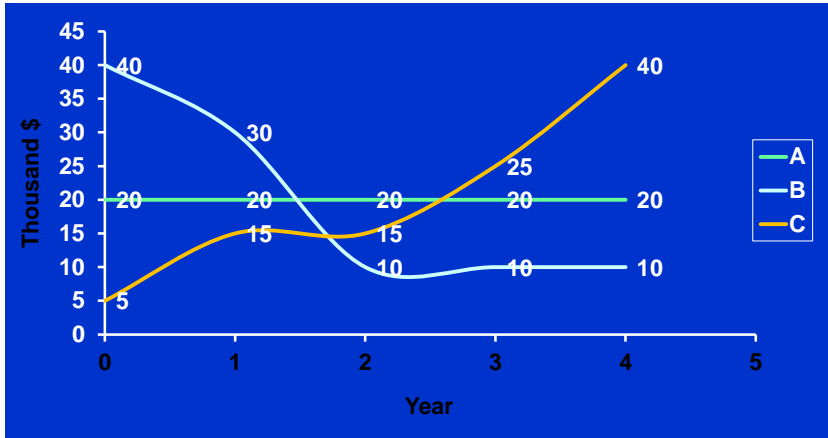
Discount rate

Report the choice of **discount rate(s) used for costs and outcomes** and say why appropriate.

Source: Husereau D, Drummond M et al. *BMC Med* 2013;11:80

Discounting example

Three programs:
cumulative investment, \$100,000 each



Discounting – why?

- **Costs and benefits of medical therapies**
 - May occur at different points in time
 - May be spread over a long period of time
- **Future costs and benefits are assigned a lower value than costs being accrued and benefits being achieved in the present**
- **Issues:**
 - What is the correct discounting factor?
 - Rationale for also discounting benefits?

CHEERS item 8

Time horizon

State the **time horizon(s)** over which costs and consequences are being evaluated and say why appropriate.

Source: Husereau D, Drummond M et al. BMC Med 2013;11:80

Often ... life-long

- Long enough to cover all relevant economic and clinical consequences of the decision to be made – life-long where relevant
- Observation time of RCTs very often NOT sufficient
- Issue of long-term treatment costs

	Total cost of trastuzumab group (EUR)	Total cost of comparator group (EUR)	Incremental cost (EUR)	LYG	Cost/ LYG (EUR)
Base case					
At 5 years	53 403	27 304	26 099	0.12	212 360
At 10 years	62 656	41 559	21 097	0.52	40 505
At 15 years	67 682	47 791	19 891	1.01	19 673

Source: Dedes K et al. Cost-effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial. Ann Oncol 2007;18:1493-9b by permission of the European Society of Medical Oncology

CHEERS item 20

Characterizing uncertainty

... Describe the **effects on the results of uncertainty** for all input parameters, and uncertainty related to the structure of the model and assumptions.

Source: Husereau D, Drummond M et al. BMC Med 2013;11:80

Uncertainty: univariate sensitivity analysis

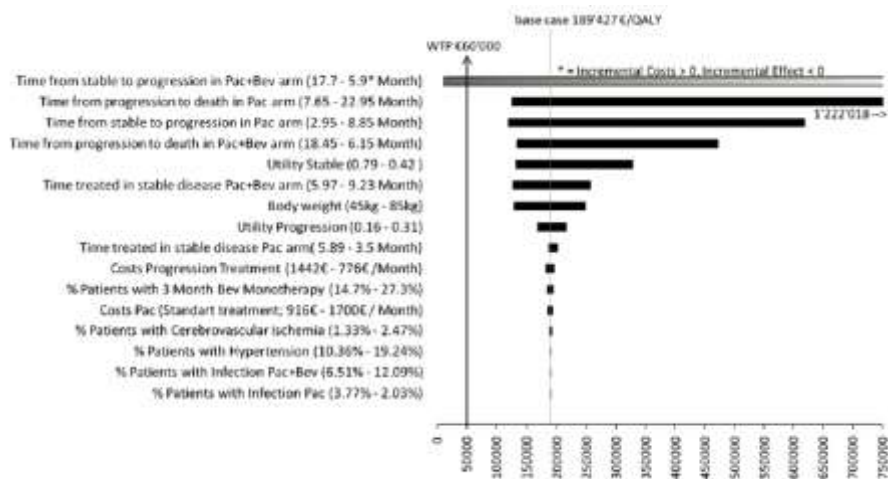
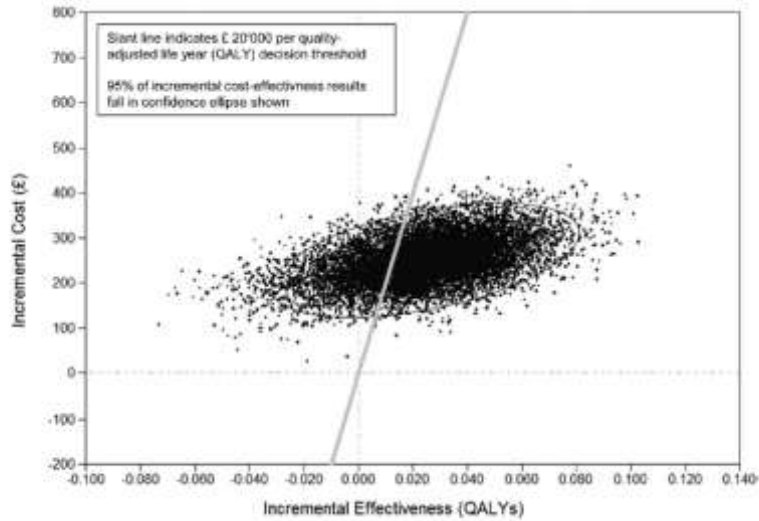


Fig. 2 - Tornado plot of the one-way sensitivity analysis for all parameters.

Source: Dedes et al. Eur J Cancer 2009;45:1397-406

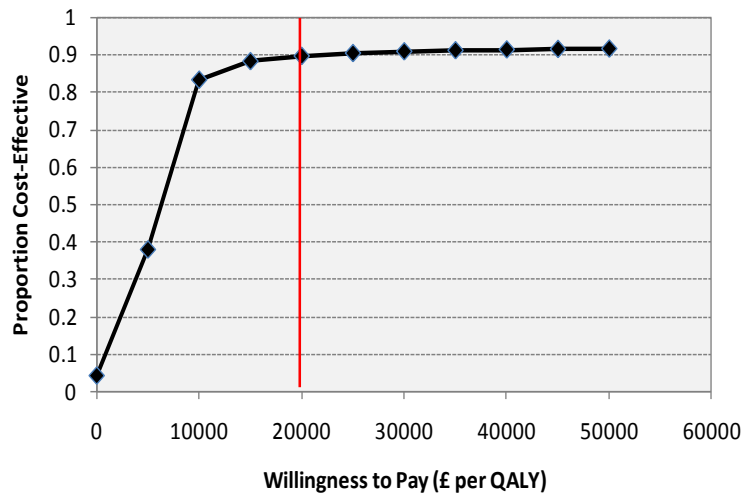
Uncertainty: probabilistic sensitivity analysis



Source: Schwenkglens et al. Value Health 2011;14:24

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Uncertainty: cost-effectiveness acceptability curve



Issues around PEE studies

- Requirement of modelling and combination of data sources
- Applicability of results to routine clinical practice?
- Time horizon often deviates from trial observation periods
- Results have short half-life
- Limited transferability
- Quality issues, lack of methodological consistency and transparency?

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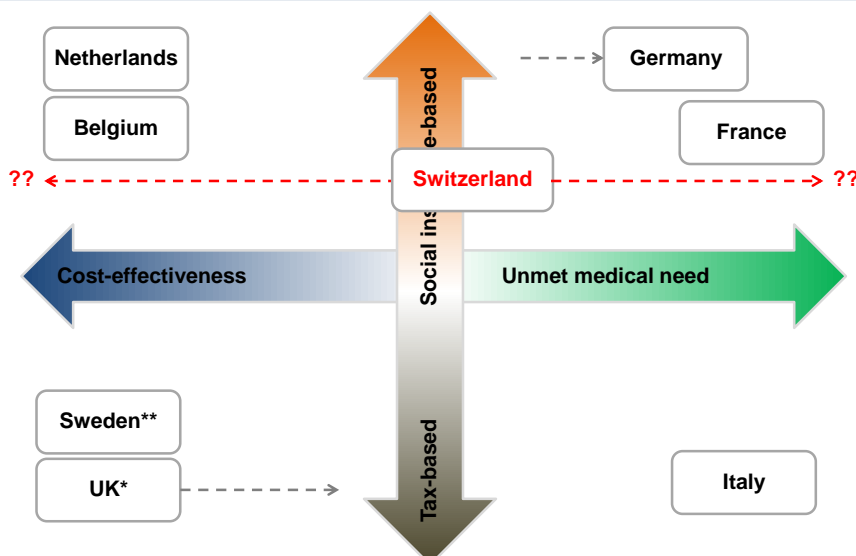
The European situation ...

- European trend to harmonise registration and marketing approval: EMA
- EU effort to lay common ground and increase joint use of information in HTA: EUnetHTA project
 - <http://www.eunethta.eu/>
- No real harmonisation is in sight at the level of health system financing and reimbursement

EMA – European Medicines Agency; EUnetHTA – European Network for Health Technology Assessment

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Use of cost-effectiveness thresholds in different countries (an incomplete picture)

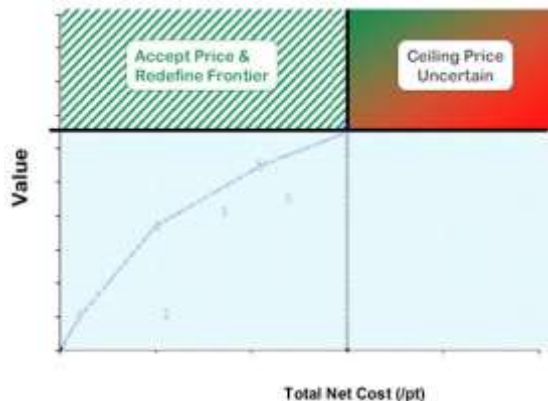


* Also Canada, Australia, New Zealand. **Societal perspective obligatory

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Germany: IQWiG approach to cost-benefit analysis

- Efficiency frontier
- Comparison within a given therapeutic area
- Measures of effectiveness may differ between areas
- New agents have to show comparable efficiency
- Deviates from gold standard approach



IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Cost-effectiveness of early assisted discharge for COPD exacerbations in The Netherlands

"RESULTS: [...] After 3 months of follow-up, differences in effectiveness [in favor of longer hospitalisation] had almost disappeared. The **difference in quality-adjusted life-years was 0.0054** (95% CI-0.021 to 0.0095). From a **health care perspective**, early assisted discharge was cost saving: [...] **-€168** (3 months, 95% CI-€1253 to €922). **Societal perspective: [...] €908** (3 months, 95% CI-€553 to €2296). The savings per quality-adjusted life-year lost were €31,111 from a health care perspective. From a societal perspective, HOSP was dominant.

Source: Goossens LM et al. Value health 2013;16:517-28

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Cost-effectiveness plane



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Cost-effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial

"RESULTS: On the basis of HERA data, our model yielded an **overall survival rate** of 71.8% for the [trastuzumab] group versus 62.8% for the control group [risk ratio (RR) = 0.87) after 10 years and **62.9% versus 52.7% (RR = 0.84) after 15 years**. Cost-effectiveness resulted in 40505 Euros (EUR) per life years gained (LYG) after 10 years and **19673 EUR per LYG after 15 years** [...]" [compared with the control group.]

Source: Dedes K et al. Ann Oncol 2007;18:1493-9

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Cost-effectiveness plane



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Cost-Effectiveness Analysis of Lapatinib in HER-2-Positive Advanced Breast Cancer

"RESULTS: **Over a lifetime**, the addition of lapatinib to capecitabine [...] was estimated to cost an additional **\$19,630**, with an expected **gain of 0.12 quality adjusted life years (QALY)** or an incremental cost-effectiveness ratio (ICER) of **\$166,113 per QALY gained**. [...] A cost-effectiveness acceptability curve indicated less than 1% probability that the ICER would be lower than **\$100,000/QALY**."

Source: Le QA and Hay JW. Cancer 2009;115:489-98

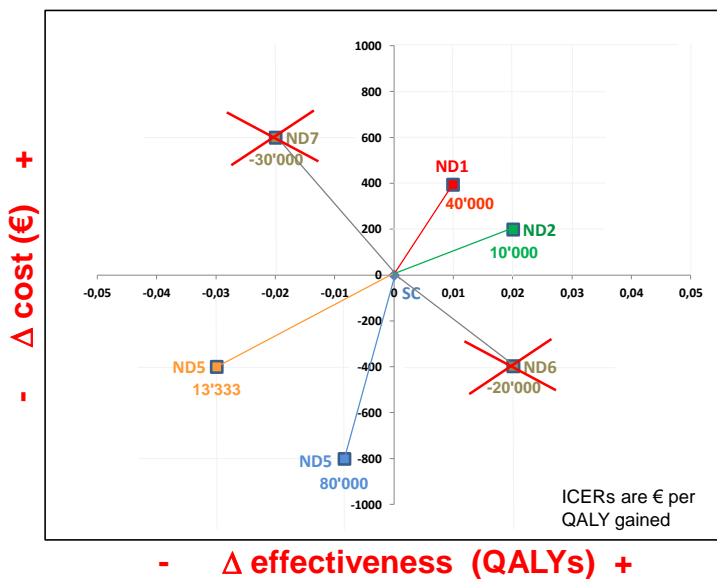
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Cost-effectiveness plane



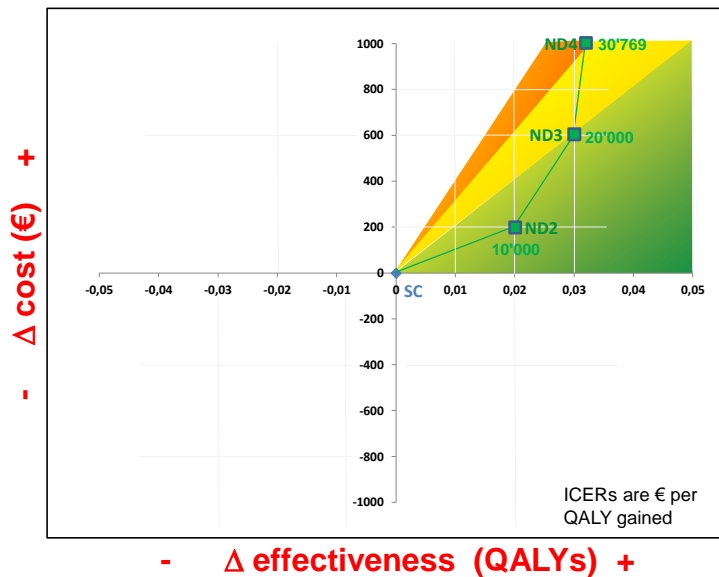
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ICER interpretation



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Which drug should be financed?



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How are cost-effectiveness thresholds set in practice?

- Arbitrarily ... some say, as a societal compromise¹
- Historically, cost of haemodialysis used as a reference point
- USA: 50'000-100'000 USD/QALY
- UK: 20'000-30'000 GBP/QALY²
- UK, highest accepted: 39'000 GBP/QALY²
(riluzole for motor neurone disease; extends tracheostomy free survival time)

¹Source: Ubel et al. Archives of Internal Medicine 2003;136:1637. ²Source: Raftery J. BMJ 2006;332:1266-8

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Source: BMJ

Risks of using cost-effectiveness thresholds for reimbursement decision-making

- In a constrained budget situation, treatments with proven cost-effectiveness may displace treatments with unknown cost-effectiveness (that may in fact be better)
- Prices may be set such that the "leeway" offered by a given threshold is exploited
- Unethical decisions may occur with 'hard' thresholds:
 - Many measures of benefit (i.e., QALYs gained) are systematically lower in some patient groups compared to others, e.g. in the elderly and in disabled persons
 - They are difficult to measure in children, person with psychiatric illness or dementia
 - Very different situations may yield identical nominal effectiveness results

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Wrap-up

- All health systems face financial constraints
- Rational allocation of resources gains in importance
- Health economic evaluation provides important information and is a key element of modern Health Technology Assessment
- Cost-utility analysis is methodological state-of-the-art, albeit not undisputed
- Improvement of methods is ongoing

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