Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

(the importance of) Economic evaluations of medical interventions: an introduction

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About the KCE (www.kce.fgov.be)

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
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OUR MISSION

KCE's mission is, on the basis of scientific analysis and research, to advise policymakers on decisions relating to health care and health insurance.

KCE is not involved in the decision-making or implementation process. Instead, its role is to identify and shed light on the best possible solutions, in the context of an accessible, high-quality health care system with due regard for growing demand and budgetary constraints. Further, KCE supports care providers by developing clinical guidelines, gearing these towards the evolving body of scientific knowledge and publishing on methodologies that serve as a guide for other health care researchers.

KCE IS INVOLVED IN FOUR MAIN DOMAINS

- Good Clinical Practice: developing clinical practice guidelines
- Health Technology Assessment: evaluating medical technologies and medicinal products
- Health Services Research: investigating the optimal means of organising and funding health care
- Methods: developing effective research instruments

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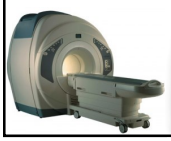
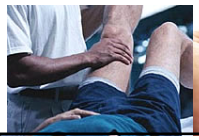
Overview

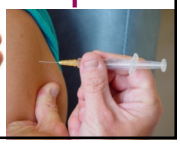
- What is HTA
  - Medical & economic part
  - GCP vs. HTA…
- What is an economic evaluation
  - Possible implications for your research
- Guidelines for economic evaluations
  - Points of attention (a first glimp…)

Health Technology Assessment

- (EUnetHTA) Definitie: "*HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.*
- *Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value.*
- *Remark: despite its policy goals, HTA must always be firmly rooted in research and the scientific method.*"

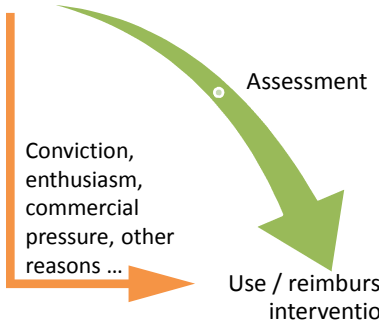




Health Technology Assessment

(innovative) intervention



(Or… no efficacy, wait and see, others…

Drug regulatory agencies and bodies such as NICE play an important part in translating research evidence into clinical guidance. It is vital that their decisions are made carefully after considering the totality of available evidence. They must be free from political, special interest, or media influence, no matter how well meaning. *The Lancet* (Editorial, 2005)

- Goal:
  Micro level: Support decision makers by providing them objective, transparent, and scientifically based information.

  Macro level:
  - Accessibility,
  - Quality,
  - Affordability (LT!), financial sustainability !

Medical part

- Medical
  - Safety
  - Efficacy
  - Effectiveness
- Economic
  - Cost-effectiveness
  - Budget impact

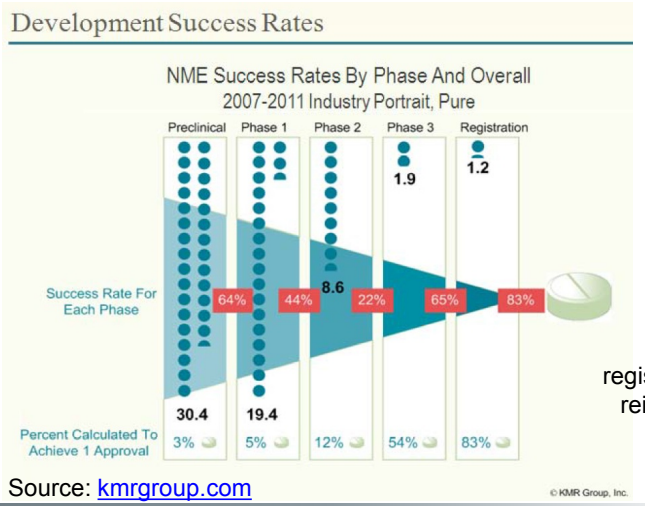
Input

E.g.:

1 INTRODUCTION
2 THE ISSUE
3 OBJECTIVES
4 GUIDELINES
5 CLINICAL EFFECTIVENESS
6 HARMS
7 COST EFFECTIVENESS OF TIOTROPIUM FOR COPD PATIENTS: A REVIEW OF THE LITERATURE
8 BELGIAN DATA
9 COST EFFECTIVENESS OF TIOTROPIUM FOR COPD PATIENTS IN THE BELGIAN CONTEXT
10 RECOMMENDATIONS

$$ICER = \frac{IC}{IE} = \frac{cost_{int.} - cost_{comp.}}{effect_{int.} - effect_{comp.}}$$

- Reasons for EBM…
  - Do you know the development success rate of new interventions?



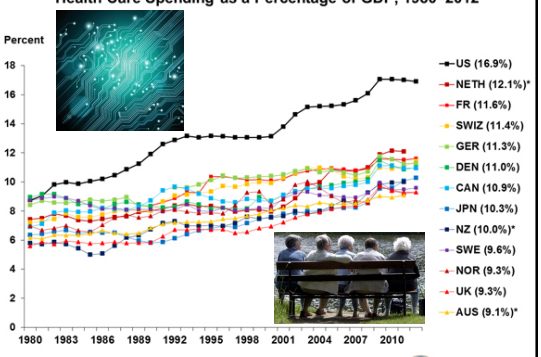
Source: kmrgroup.com

Remark: registration versus reimbursement

Economic part

- Limited resources
- Opportunity costs

Health Care Spending as a Percentage of GDP, 1980–2012



* 2011.
GDP refers to gross domestic product.
Source: OECD Health Data 2014.

The Commonwealth Fund

- "How much will Herceptin really cost?" (Barrett, BMJ, 2006)

Table 1 Cost and potential benefits of adjuvant cancer treatments in Norfolk and Norwich University Hospital Trust

Treatment	No of patients given treatment	Drug cost (£000)	Proven benefit	Potential benefit at our hospital	Cost per patient cured (£000)
Adjuvant chemotherapy for lung cancer	15	23	5-15% improved 5 year overall survival[w3]	1 extra patient cured	23
Oxaliplatin as adjuvant therapy for colon cancer compared with fluorouracil alone	20	137	5% improved 3 year disease-free survival; no benefit to overall survival[w4]	1 extra patient without recurrence at 3 years	137
Neoadjuvant chemotherapy for oesophageal cancer	25	8	9% improved 5 year survival[w5]	3 extra patients cured	2.67
Rituximab in addition to CHOP for non-Hodgkin lymphoma in patients over 60	25	215	13% improved 2 year overall survival[w6]	3 extra patients cured	71.67
Adjuvant aromatase inhibitors in postmenopausal breast cancer	270	120	3.7% improved disease-free survival compared with tamoxifen; no benefit to overall survival[w7]	8 extra patients without recurrence at 5 years	15
Total	355	503		16 extra patients cured	
Herceptin for early stage breast cancer	75	1940	0-4% improved 4 year overall survival[w1 w2]	3 extra patients cured	650

CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone.

Market Spiral Pricing of Cancer Drugs

Light, Cancer, 2013

Every patient with cancer or another life-threatening disease wants the most effective treatment, but drug prices have become staggering. Twelve of the 13 new cancer drugs approved last year were priced above $100,000 annually (Table 1),

The added-value argument for unaffordable prices is not supported by objective data. Most new cancer drugs provide few or no clinical advantages over existing ones. Only one of the 12 new anticancer drugs approved in 2012 provides survival gains that last more than 2 months (Table 1).

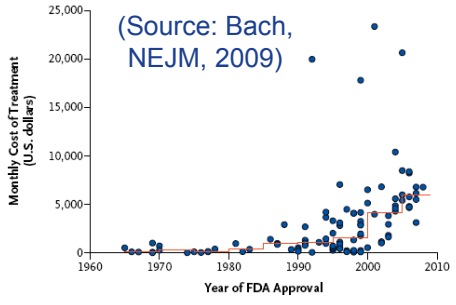


Figure 1. Monthly and Median Costs of Cancer Drugs at the Time of Approval by the Food and Drug Administration (FDA), from 1965 through 2008.

Shown are costs for 1 month of cancer treatment for a person who weighs 70 kg or has a body-surface area of 1.7 m². The red line indicates median prices during a 5-year period. Prices have been adjusted to 2007 dollars and reflect the total price for the drug at the time of approval, including both the amount of Medicare reimbursement and the amount paid by the patient or by a secondary payer. (For details about the costs of individual drugs, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

In 2012:

Drug (Trade Name; Company)	Monthly or Per-Cycle Cost
Axitinib (Inlyta; Pfizer)	$10,584 (up to $21,168)/mo
Enzalutamide (Xtandi; Astellas)	$8,940/mo
Ziv-aflibercept (Zaltrap; Sanofi-Aventis)	$15,360/mo (two 200-mg vials per dose; 80 kg)
Regorafenib (Stivarga; Bayer)	$11,220/mo
Pertuzumab (Perjeta; Genentech)	$4,890/3 weeks
Cabozantinib (Cometriq; Exelixis)	$11,880/mo
Vismodegib (Erivedge; Genentech)	$9,000/mo
Carfilzomib (Kyprolis; Onyx)	$11,937/mo (1.8 m²)
Bosutinib (Bosulif; Pfizer)	$9,817/mo
Ponatinib (Iclusig; ARIAD)	$12,900/mo
Omacetaxine (Synribo; Teva)	$28,056/mo for 14-day cycles; $14,028/mo for 7-day cycles (1.8 m²)
Vincristine sulfate liposome (Marqibo; Talon)	≈$12,000/cycle
Glucarpidase (Voraxase; BTG International)	$108,000 (80 kg)

Medical vs Medical/economic

The Doctor's Dilemma — What Is "Appropriate" Care?

of which is the "primacy of patient welfare." It also sets out 10 "commitments," one of which states that "while meeting the needs of individual patients, physicians are required to provide health care that is based on the wise and cost-effective management of limited clinical resources." How can a commitment to cost-effective care be reconciled with a fundamental principle of primacy of patient welfare?

Physician (CPG)

- Patient
- Effectiveness
- Disease-oriented evidence, ST-studies, surrogate endpoints, expert opinion, …

Patient / Tax payer

Payer (HTA)

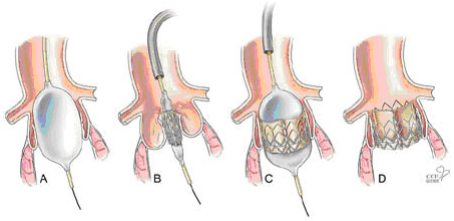
- Society
- Efficiency (cost-effectiveness) ≠ cost cutting!
- Patient-oriented evidence, LT-horizon, endpoints: mortality (life-years gained) & QoL

De PARTNER cohorte A-data bewijzen dat, in een hoogrisicopopulatie met ernstige aortaklepstenose, zowel transfemorale als transapicale TAVI een equivalent alternatief is voor chirurgische aortaklepvervanging. Er bestaat geen twijfel over dat TAVI het chirurgisch 'trauma' reduceert en minstens op middellange termijn een waardevol alternatief biedt. Dit bevestigt feitelijk de klinische praktijk die de laatste jaren meer en meer in voege is bij behandeling van deze patiëntenpopulatie. Hiertegenover staat wel opnieuw een wat verhoogd risico op stroke, wat natuurlijk met de individuele patiënt besproken en afgewogen moet worden.

gegeven. Ondanks de hoge kostprijs van de techniek speelt bovendien nu, naar mijn mening, het ethische aspect een zeer belangrijke rol, aangezien zonder TAVI veel hoogrisicopatiënten met ernstige aortaklepstenose, die geen optimale chirurgische kandidaten meer zijn, vroegtijdig zullen overlijden wanneer hun TAVI onthouden wordt. Merk op

(Tijdschr. Card., 2011)

E.g.: TAVI



- Equivalent alternative
- Less invasive
- Clinical practice
- Stroke risk
- Higher costs

Contradiction?

Table II Recommendations for the use of transcatheter aortic valve implantation

Recommendations	Class[a]	Level[b]	Ref[c]
TAVI should only be undertaken with a multidisciplinary 'heart team' including cardiologists and cardiac surgeons and other specialists if necessary.	I	C	
TAVI should only be performed in hospitals with cardiac surgery on-site.	I	C	
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a 'heart team' and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities.	I	B	99
TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a 'heart team' based on the individual risk profile and anatomic suitability.	IIa	B	97

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

No reimbursement (based on HTA)

Source: Guidelines on the management of valvular heart disease, European Heart Journal (2012)

E.g.: TAVI: the evidence (in 2011)

- High-risk ptn (←→ inoperable)

  TAVI vs. Surgical aortic valve replacement (sAVR)

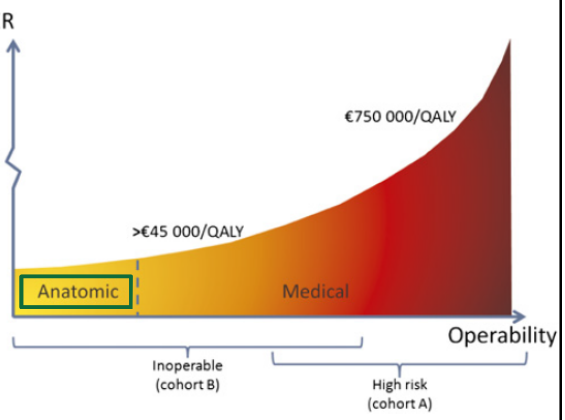
  - Equal mortality after 1 year (24.2% vs. 26.8%, p=0.44)
  - No improvement in HRQoL after 1 year
  - Doubling risk of stroke (8.3% vs. 4.3%, p=0.04)
  - Price: TAVI: >€40.000
    sAVR: ±€24.000
    (IC! + context-specific)

Physician / patient

Government / tax payer

E.g.: TAVI

- Extra details:
  - **Full HTA report: Neyt M, Van Brabandt H, Van de Sande S, et al. Health Technology Assessment. Transcatheter Aortic Valve Implantation (TAVI): A Health Technology Assessment Update. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE), 2011.**
  - **Neyt et al., BMJ Open, 2012**



Introduction economic evaluations

- Why economic evaluations:
  "*Economic evaluation techniques tend to guide decision makers towards the maximisation of health gains within a resource constraint, regardless of which individuals or population groups may benefit from a health intervention or perhaps be penalised by that intervention.*" (Sassi et al, 2001)
- Remark: one of the criteria… (see next slides)

Economic evaluations in Belgium

- For class 1 pharmaceuticals (CRM, Commission Reimbursement of Medicines)

Art. 4. De beslissing omtrent het al dan niet opnemen, het wijzigen of het schrappen omvat een beslissing over de vergoedingsbasis, de vergoedingsvoorwaarden, de vergoedingscategorie en de vergoedingsgroep en gebeurt na een evaluatie van één of meer van de volgende criteria, zoals bepaald in artikel 6 : (KB, 21 december 2001)

Class 1: crit. 1-5
Class 2: crit. 1-4
Class 3: crit. 2 & 4

Art. 6. Indien een specialiteit door de aanvrager gerangschikt is in klasse 1 worden alle criteria vermeld in artikel 4 in de beoordeling gehanteerd. Indien een specialiteit door de aanvrager gerangschikt is in klasse 2 worden de criteria vermeld in artikel 4, 1° tot en met 4° in de beoordeling gehanteerd. Indien een specialiteit door de aanvrager gerangschikt is in klasse 3 worden de criteria vermeld in artikel 4, 2° en 4° in de beoordeling gehanteerd.

1° De therapeutische waarde	1° Therapeutic value
2° De prijs van de specialiteit en de door de aanvrager voorgestelde vergoedingsbasis	2° price
3° Het belang van de specialiteit in de medische praktijk in functie van de therapeutische en sociale behoeften	3° importance in medical practice
4° De budgettaire weerslag voor de verzekering, rekening houdend met de begrotingsdoelstellingen	4° budget impact
5° De verhouding tussen de kosten voor de verzekering en de therapeutische waarde.	5° cost effectiveness

Class 1

Economic evaluations in Belgium

- Also for devices! (Commission for Reimbursement of Implants and Invasive Medical Devices)

1° Therapeutic value
2° price
3° importance in medical practice
4° budget impact
5° cost effectiveness

Art. 16. De beslissing met betrekking tot de aanvraag tot aanpassing van de lijst wordt door de Minister genomen, na een evaluatie van één of meerdere van de volgende criteria bedoeld in artikel 35*septies*/2, § 3, van de wet :

1° de therapeutische waarde van het hulpmiddel, uitgedrukt in één van de twee klassen die uitgebreid worden gedefinieerd in artikel 17;

2° de individuele prijs van het hulpmiddel, en de voorgestelde vergoedingsbasis;

3° het belang van het hulpmiddel in de medische praktijk in functie van de therapeutische en sociale noden;

4° de budgettaire weerslag voor de verzekering;

5° de verhouding tussen de kosten voor de verzekering en de therapeutische waarde van het hulpmiddel.

Class 1

Art. 17. De therapeutische waarde en de eventuele therapeutische of gezondheidseconomische meerwaarde van een hulpmiddel worden uitgedrukt in één van de volgende klassen :

1° Klasse 1 : hulpmiddel met een aangetoonde meerwaarde tegenover bestaande therapeutische alternatieven.

...

Art. 18. § 1. Indien in de aanvraag tot aanpassing een hulpmiddel wordt gerangschikt in klasse 1, worden alle criteria vermeld in artikel 16 in de beoordeling gehanteerd.

...

(Belgian Monitor, 1 July 2014)

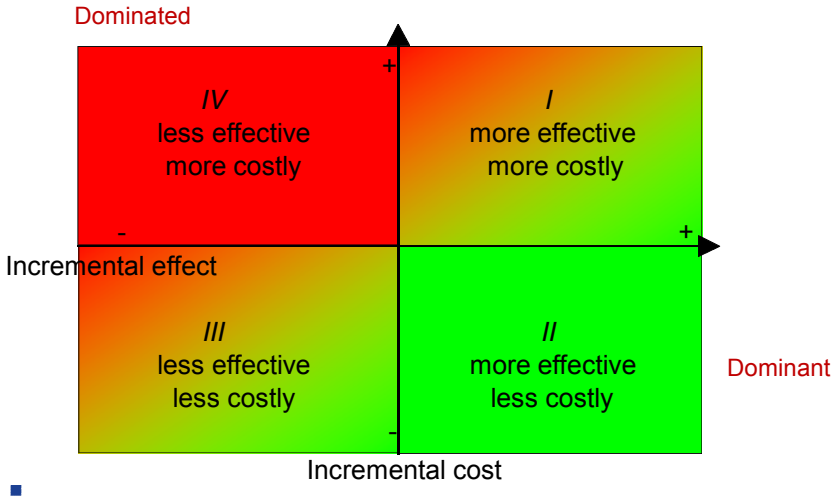
Introduction economic evaluations

- What: "economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences." (Drummond, 2005)
- Outcomes:
  "incremental cost-effectiveness ratio" (ICER)

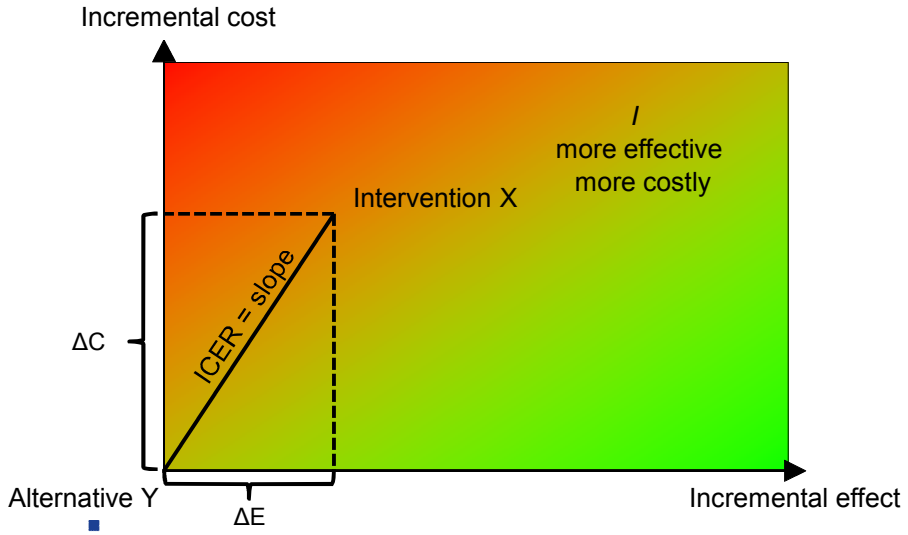
$$ICER = \frac{IC}{IE} = \frac{cost_{int.} - cost_{comp.}}{effect_{int.} - effect_{comp.}}$$

- ➔ € per LYG ("life-year gained")
  ➔ € per QALY gained ("quality-adjusted life-year gained")
- Comparison across indications…

Cost-effectiveness plane



Cost-effectiveness plane



Full economic evaluations

CMA	Cost-minimization analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
~~CBA~~	Cost-benefit analysis
CCA	Cost-consequences analysis

Open question

- Which elements would you include in your research if you would like to perform an economic evaluation in the future?

ST *C&E (+/-)* LT

- Where, when & how are you going to gather this information…

Mortality 30-day end follow-up extrapolation?

Immediate short term medium term long term

Uncertainty ~ scenario-analyses

Follow-up

Re-hospitalisation

Guidelines

- KCE & EUnetHTA documents:
  - Cleemput I, Neyt M, Van de Sande S, Thiry N. Belgian guidelines for economic evaluations and budget impact analyses: second edition. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre(KCE). 2012. KCE Report 183C.
  - EUnetHTA: Methods for health economic evaluations (May 2015)
  - EUnetHTA: Endpoints used for relative effectiveness assessment of pharmaceuticals: HRQoL and utility measures (February 2013)

Reasons for guidelines (to whom)

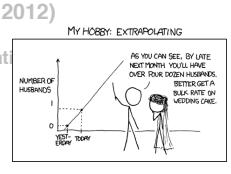
- "Assist the "doers" of economic evaluations (i.e., analysts) to produce credible and standardized economic information that is relevant and useful to decision makers." (CADTH, 2006)
- Assist policy makers
  - The guidelines for economic evaluations can help to improve the transparency and quality of economic evaluations.
    - Which will be beneficial for the critical appraisal of the files.
    - Accelerate review process
- Also to assist researchers!

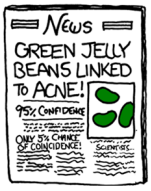
RESEARCH PROTOCOL

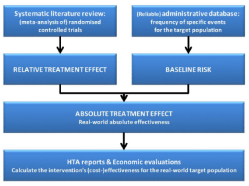
Be aware of several points of attention

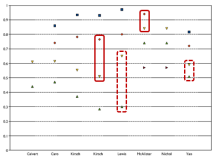
- KCE guidelines (report 183, 2012)
  - 1) Literature review
  - 2) Perspective of the evaluati
  - 3) Target population
  - 4) Comparators
  - 5) Analytic techni
  - 6) Study d
  - 7) Calc
  - 8) Estimation/valuation of outcomes
  - 9) Time horizon
  - 10) Modelling
  - 11) Handling uncertainty
  - 12) Discount rate
  - 13) Budget impact analyses

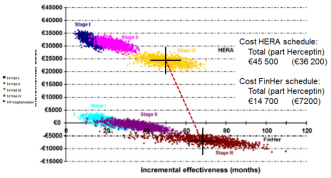
REFERENCE CASE











"Summary by a single number loses the richness of all that data underneath"
(Bhumbra, BMJ, 2012)

Subgroup analysis

Statistically justified

- ~Results trials (e.g. trastuzumab & LVEF)
- Differences in safety, effects or costs between clearly defined subgroups.
- Remark: post-hoc subgroup analysis (see next slide)

Difference in baseline risk

- "*Often the clinical report of a trial will indicate that there is no evidence of differences between subgroups in terms of relative treatment effect. However, cost-effectiveness is driven by absolute benefit, and there may still be important variation between subgroups in baseline event rates.*" (Drummond, 2005)

Baseline risk

- Example:
  - Percentage of patients who progress to metastasis (~baseline risk)

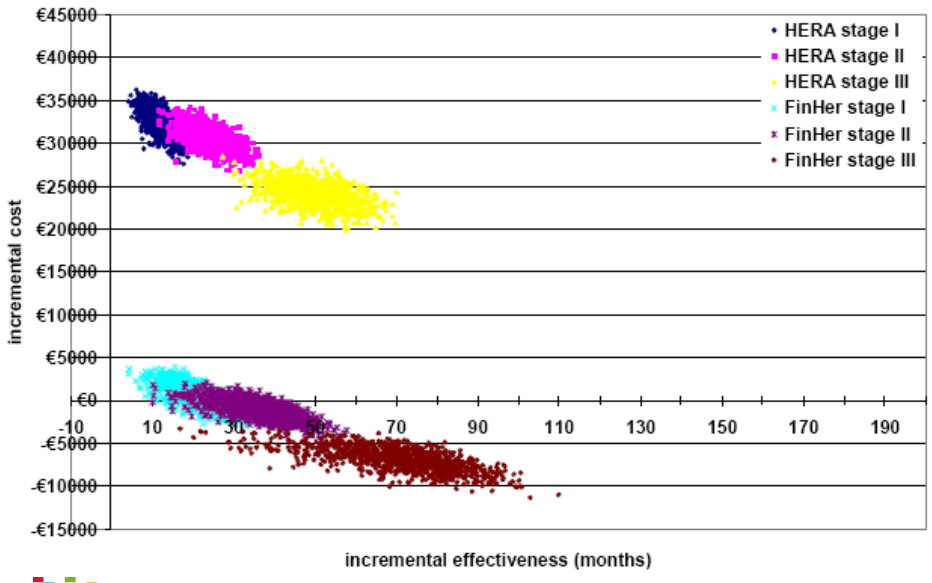
	<50	50-59	60-69	70-79	80+	All
Stage I	47%	39%	31%	23%	14%	32%
Stage II	61%	54%	46%	38%	26%	46%
Stage III	81%	78%	74%	66%	51%	72%

Source: Berkowitz, 2000

  - All subgroups 50% relative improvement with new intervention

	<50	50-59	60-69	70-79	80+	All
Stage I	23,5ppt	19,5ppt	15,5ppt	11,5ppt	7ppt	16ppt
Stage II	30,5ppt	27ppt	23ppt	19ppt	13ppt	23ppt
Stage III	40,5ppt	39ppt	37ppt	33ppt	25,5ppt	36ppt

Figure 10. Cost-effectiveness plane HERA versus FinHer trial (stage I, II, and III; all patients)



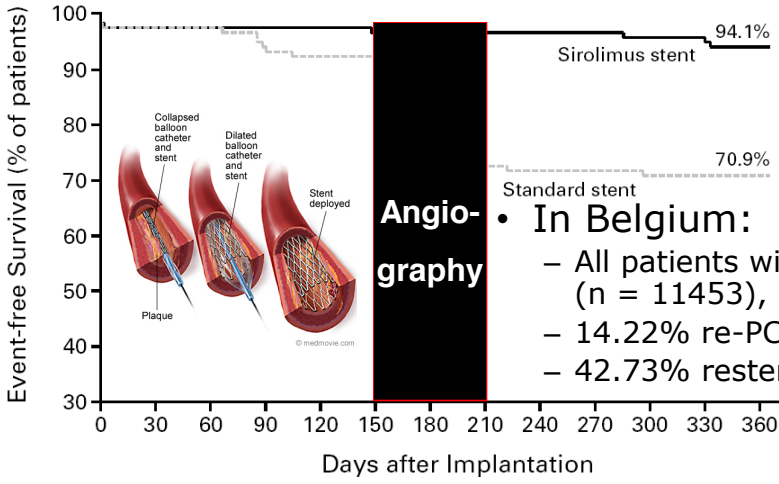
Baseline risk

- Trial results ←→ real-world circumstances
  - E.g. 1: DES & re-interventions
    - RCTs & protocol-driven angiographic follow-up

    (Neyt et al., PharmacoEconomics, 2009)
  - E.g. 2: Tiotropium (COPD)
    - High-risk RCT population

E.g. 1: Trial vs real-world (DES)

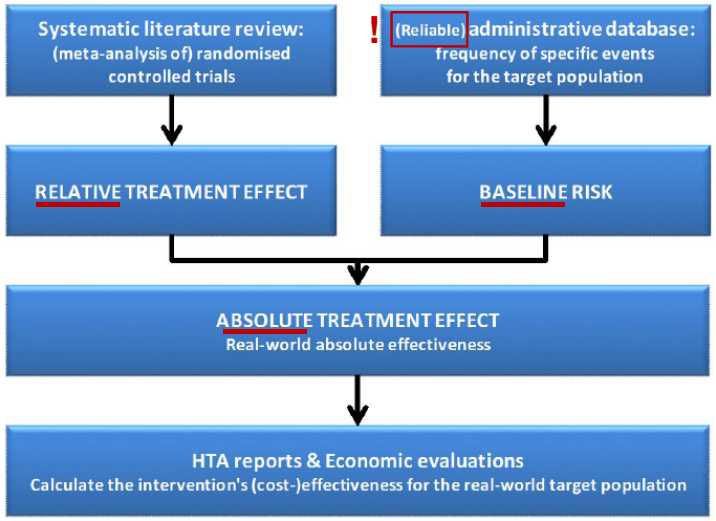
Figure: Morice, NEJM, 2002 (RAVEL)



- In Belgium:
  - All patients with BMS (n = 11453),
  - 14.22% re-PCI
  - 42.73% restenosis

- Possible approach: Combine strengths of both RCTs and observational data…

Source: Neyt et al., Health Policy, 2012



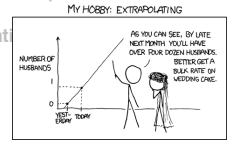
…

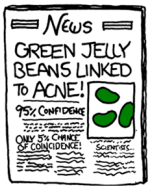
- What do you prefer?
  - Halving of mortality &
  - 4% increase of adverse events
    OR
  - Decrease in mortality of 0,5% &
  - Fivefold increase in adverse events

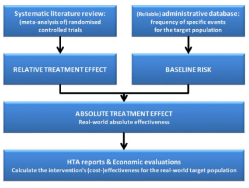
Be aware of several points of attention

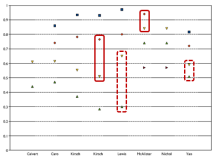
- KCE guidelines (report 183, 2012)
  - 1) Literature review
  - 2) Perspective of the evaluati
  - 3) Target population
  - 4) Comparators
  - 5) Analytic techni
  - 6) Study d
  - 7) Calc of costs
  - 8) mation/valuation of outcomes
  - 9) Time horizon
  - 10) Modelling
  - 11) Handling uncertainty
  - 12) Discount rate
  - 13) Budget impact analyses

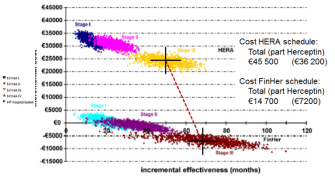
REFERENCE CASE











"Summary by a single number loses the richness of all that data underneath"
(Bhumbra, BMJ, 2012)

Questions or remarks…

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Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

- ME-TA: mattias.neyt@me-ta.eu
  FYI: 3-day training "economic evaluations of medical interventions"
  20-22 April, 2016 (St.-M.-Latem)
  14-16 September, 2016 (Leuven)

ME-TA
Medical Evaluation Technology Assessment

To remember

- What is HTA
  - Importance of medical/economic part
  - Different perspectives
- Why economic evaluations
- Which elements are of importance…
- Guidelines
  - KCE guidelines (& points of attention…)
  - EUnetHTA guidelines (HRQoL)

Own research + interpretation/ critical assessment of other evaluations