

**THE APPROPRIATENESS OF THE COST PER QALY
IN THE DECISION-MAKING PROCESS**

Madrid, Spain
November 5-8, 2011

Mark Nuijten
Dominique Dubois
Gerry Oster

Methodological Issues

Issues:

- Quality of life. Is it all about QALY's?
- Discounting
- Utility concept
- Dealing with uncertainty
- Perspective and time horizon
- Data collection and validity
- Costing
- Design

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BACKGROUND

Introduction



Trends for Pharmaceuticals



Methodological Concepts

Utility - QALY

- Survival, but also correction for Quality of Life
- Final (hard) endpoint between 0 and 1:
 - > Dead: 0
 - > Perfect health: 1

	Survival	Quality of Life	QALY
Treatment A	8	0.5	4.0
Treatment B	5	0.9	4.5

- Comparison across diseases

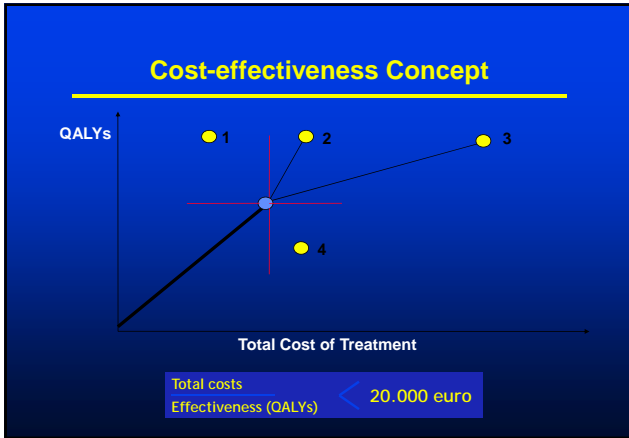
Methodological Concepts

Cost-effectiveness:

- Incremental cost-effectiveness ratio - Cost per QALY

	Survival	Quality of Life	QALY	Total costs	ICER
Treatment A	8	0.5	4.0	1000	
Treatment B	5	0.9	4.5	1500	
Difference			0.5	500	1000

- Interpretation: Extra Euro 1,000 to gain one year in perfect health!



- ### Focus
- #### Concerns ICER
- Methodological concerns
 - Other concerns
 - Ethical
 - Equity
 - Broader concerns
 - Alternatives

- ### Methodological Issues
- #### Issues:
- Discounting
 - Utility concept
 - Dealing with uncertainty
 - Perspective and time horizon
 - Data collection and validity
 - Costing
 - Design

CONSIDERATIONS

Considerations

Main considerations:

- Methodological concerns of cost-effectiveness data



What is accuracy of cost-effectiveness outcome?

- Treatment A: 25,000 Euro/QALY
- Treatment B: 30,000 Euro/QALY
- What is justification of threshold, e.g. 20,000 Euro/QALY?
- Does cost-effectiveness capture all societal preferences for selecting priorities in the decision making process, especially innovation.

Methodological Issues

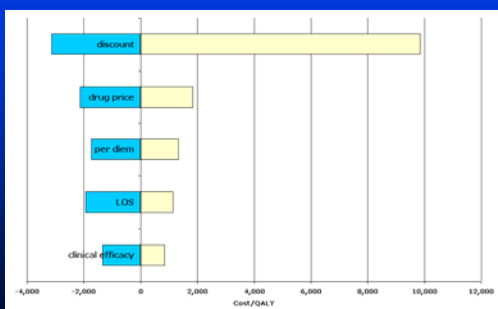
Discounting: example

Discount	Costs	Effectiveness	Outcomes	ICER	Threshold	Decision
4%	€3,007	1.50%	0.27	€11,137	< 20,000	YES
4%	€3,007	4.00%	0.14	€21,479	> 20,000	NO
3.5%	€3,007	3.5%	0.17	€17,688	< 20,000	YES



Decision can depend on discount rate

Methodological Issues



Methodological Issues

Discounting: policy and ethical

- Different rates for discounting:
 - Absolute differences between countries
 - Different rates effectiveness
 - Cost/QALY different → different decision
 - Different decision for reimbursement
 - Inequal access patients in Europe only due discount rate
- ethical ?

Methodological Issues

Discounting: other discussions

- Different time preferences for different goods: health \neq cost
- Health and money are not logically 1 to 1 directly related
- Discount rates for health are likely to differ for different health benefits
- Time preferences for health might be caused by different mechanisms, since single entity of a life cannot be viewed with ignoring the rest of the life that continues
- Validity of constant discounting is questioned: life cannot simple be cut into life years as single entities

Methodological Issues

Utility:

- Final (hard) endpoint
- Comparison across diseases
- Cost per QALY
 - Euro 10,000 per stroke vs. Euro 5,000 per life year saved ?

Methodological Issues

Utility - QALY:

- Concept:
 - Is QALY a measure of social value ?
 - Includes fairness and equity ?
 - Each person's life year is equally important?
- Measurement - no consensus on:
 - Varies scales (e.g. STG, TTO) yield widely different results
 - Constructing scenarios on health status (brief to detailed)
 - Whose values ?

Methodological Issues

Utility: other issues

- Adjustment for severity of disease (Netherlands)
- Adjustment for age (UK)
- Aggregation problem: different individual values in one aggregate value
- Society perspective: no comparison outside health
 - Education
 - Public transport

Methodological Issues

Costing:

- Opportunity cost: value of value that good or service in its next best use.

BUT:

- No market place is perfect, especially not health care market:
 - Information assymetry
 - Market distortions
 - Cross-subsidies
- Prices (charges and reimbursement): only “proxy” costs.
- No consensus on methods for converting charges to better reflects costs.

Methodological Issues

Costing:

- Sources: not organised for research.
 - Decentralisation of cost information
 - Lack of reserach-based coding dictionary.
 - Risk of inaccurate costing
 - Cost driver → high impact on cost/QALY
- Hospitalisation often cost driver, but often missing in databases!

Methodological Issues

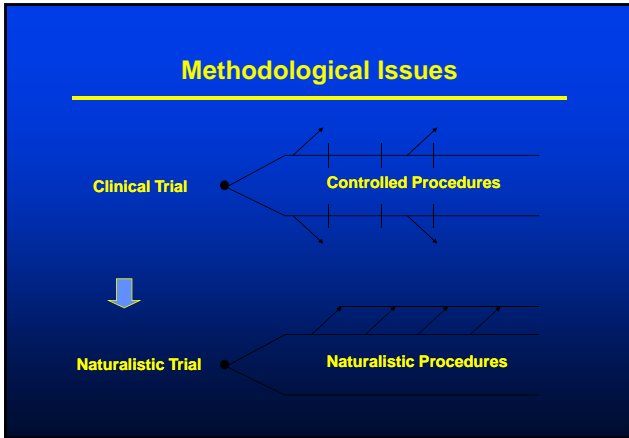
Perspective and time horizon

- Society vs. health authorities
 - How to compare: Netherlands (society) vs. UK (NHS)
 - Cost/QALY different → different decision
 - Unequal access patients due to perspective → ethical ?
- Time horizon:
 - > clinical trial period → extrapolation and modelling
 - Chronic diseases → no consensus:
 - ✓ 5-year ? Euro 10,000/QALY
 - ✓ 10 year ? Euro 7,000/QALY
 - ✓ life time analysis ? Euro 3,000/QALY
 - Which Euro/QALY should be used ?
 - Conceptual - life time ? BUT extra uncertainty

Methodological Issues

Collecting data on health care utilisation

- Sources:
 - RCT – piggy back
 - Naturalistic studies
 - Observational studies – registers
 - Patient records
 - Delphi panels
- Concerns:
 - External validity – daily practice
 - Confounding variables
 - Missing data indirect cost, non-medicals costs
- More research needed to validate the accuracy of the different sources

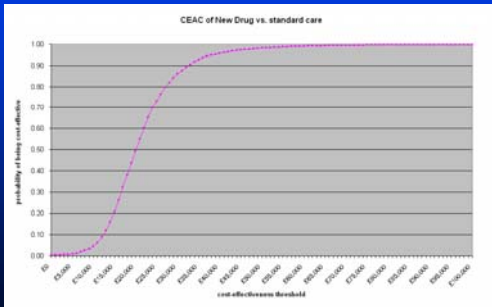


- ### Data Collection
-
- Modelling study:**
- Simulation and valuation of clinical events based on available data from various sources.
 - Opportunities: solving constraints of prospective studies:
 - Long-term follow-up (extrapolation)
 - Selection of appropriate comparaton
 - Inclusion of treatment failures
 - Increasing acceptability for reimbursement dossiers

- ### Methodological Issues
-
- Costing:**
- Types of costs to be included (Eichert):
 - Cost related to disease
OR
 - Costs resulting from any change in mortality
 - Exclusion indirect medical costs affect ICER

- ### Methodological Issues
-
- Dealing with uncertainty**
- Interval ICER
 - Standard parametric assumption is controversial
 - Various methods for approximating parametric confidence intervals (O, Brien, Wakker)
 - Uncertainty > 1 quadrant
 - Alternative: C-E acceptability curve concept (AI, Van Hout)
 - Probabilistic information more useful than confidence intervals ?
 - Appropriate interpretation by decision makers ?

Methodological Issues



Methodological Issues

Dealing uncertainty - models

- Lack of appropriate distributions for critical variables
- Other uncertainty
 - Conflicting data from the literature
 - Lack of appropriate data sources
 - Confounding variables in data source – observational studies
 - Structure and assumptions

THRESHOLD

Concept of a Threshold

- Concept refers to the level of costs and effects that an intervention must achieve to be acceptable in a given health-care system.
- Implicit vs. explicit threshold:
 - Explicit: A group of decision-makers formally adopt and make public in advance any threshold by which their decision on resource allocation would be bound
 - Implicit: 1) not public or official, 2) may be inferred by retrospective analysis of assessments
- Soft vs hard threshold: next slide

Concept of a Threshold

- Hard threshold: dictates that results from CE analysis become the sole decision criterion for resource allocation:
 - Cost/QALY is sole criterion for resource use allocation
 - Pros: transparency, consistency and predictability
 - Cons: incorporating non-CE based societal preferences
- Soft threshold: 1) threshold with lower and upper boundaries, 2) allows to include also other decision influencing factors such as equity or others.
 - < minimum: always approval
 - > maximum: never approval
 - “smudge”: depends on other criteria.

Threshold Data

Literature

- Kaplan & Bush, USA (1982):
\$50,000 / QALY
“dialysis standard”
- Laupacis et al., Canada (1992):
lower bound : ≈ €20,000 / QALY*
upper bound: ≈ €100,000 / QALY
- WHO (2002): 3 x GDP per capita / DALY
- Sacristána et al., Spain (2002): €22,500 / Life Year gained *

*: inflated to 2006, converted to €

Implicitly used

- Retrospective analyses of past (drug) reimbursement decisions:
 - AUS (PBAC past decisions):
lower boundary: ≈ €32,000 / LYG*
upper boundary: ≈ €57,000 / LYG*
 - UK (NICE past decisions):
lower boundary : ≈ €36,000 / QALY*
upper boundary: ≈ €54,000 / QALY*

*: inflated to 2006, converted to €

Cost-effectiveness League Table

Intervention	Cost per QALY (\$)
Pacemaker implantation	1.400
Hip replacement	1.500
Valve replacement	1.800
CABG, moderate AP, LM	2.000
CABG, moderate AP, 3VD	4.000
CABG, moderate AP, 2VD	5.100
PTCA, moderate AP, 1VD	6.000
Heart transplantation	10.000
Maximum WTP per QALY	10.000
CABG, moderate AP, 1VD	12.000
Hemodialysis at home	22.000
Hemodialysis in hospital	28.000

Threshold

What is the basis for thresholds in the literature?

- 50,000 US \$ / QALY ¹ been quoted for many years as threshold in the US
 - „Based“ on the dialysis standard, the purported annual cost/QALY on the Medicare program for patients with chronic renal failure
 - This often cited „standard“ might have been based on considerable underestimation of the program’s true costs¹
 - Basis from 1982 (!!) – „threshold“ was never adjusted by inflation
- Laupacis et al.² in Canada (in 1990 CAN \$): 20,000 – 100,000 CAN \$ / QALY
 - Authors mentioned, that these boundaries were arbitrary but in line with what had been universally accepted

Threshold

What is the basis for thresholds in the literature?

- Goldman et al. (1996) summarized assessment for cardiovascular interventions:
 - Maximum of 40,000 US \$ / life year gained, which roughly corresponds to renal dialysis from 1982 (!)
 - Basis from 1982 (!) – „threshold“ was never adjusted by inflation
- Newhouse et al. (1998) surveyed health economists:
 - Reported mean value of 60,000 US \$ / life year gained
 - Biased when asking open-ended questions

Threshold

What is the basis for thresholds used implicitly?

- World Health Report 2002 ¹ “...The recent report of the Commission on Macroeconomics and Health suggested that interventions costing less than three times GDP per capita for each DALY averted represented good value for money.” ²
 - Based on expected direct and indirect costs for the economy, whereas no specification of the types of costs that should be considered is provided
 - Why three times GDP? No theoretical or empirical basis
- Based on this recommendation the CE threshold should be in Germany around \$ 90,300 (GDP - per capita - PPP), which is around €70,000.

Threshold

UK:

- Retrospective analysis: approval
 - GBP 30,000
 - > 30,000 ⇒ special factors and not covered by formal modelling
- Nice (2004):
 - < 20,000: likely
 - 20 – 30,000: other factors innovative nature of the therapy
 - Case: 36,000 risk sharing agreement with industry for MS

Threshold

Huge differences per country:

- Netherlands: € 20,000
 - UK: € 36,000 – € 54,000
- ↓
- Unequal access patients in Europe only due threshold
- ↓
- ethical ?
- legal (EU law) ?

Threshold

Who sets threshold?

- NICE: Threshold searcher for optimal threshold between:
 - Least cost-effective technology currently provided
 - Most cost-effective technology not yet available
- Nice (2004): Determination of budget is task of Parliament, not NICE:
 - Relative value of public money spent on health care versus education, defence environment
 - Since determining threshold is logically equivalent to determining the budget
 - ↓
 - WTP for QALY could only be given by NICE, if responsibility for NHS budget

Threshold

Considerations:

- Only valid under assumptions: perfect divisibility of health care programs, constant returns to scale and constant marginal opportunity costs (Birch) ⇒ not true
- Use of threshold may lead to uncontrolled growth of health care expenditure
- Thresholds ignore that health care systems are resource constrained

	Cost-effectiveness		
	Extra Costs	Extra QALY	ICER
Program A	100	0.5	200
Program B	1000	5	200
Extra costs	900		

Threshold

- Other considerations (Eichler):
 - Reduced burden of responsibility upon those who previously made implicit rationing decisions alone.
 - Better consistency and transparency, equity and public trust
 - Politically sensitive
 - Decision maker is not economist: reluctant to base decision on one measure alone
 - Not using allows room for arbitrariness and “ad hoc” considerations

Threshold

Two options (Eichler):

- CE ratio determines budget OR
- Budget determines CE ratio
- BUT: not at the same time (Karlsson)
 - ↓
- Health care budgets are NOT fixed (not in long-term)
 - Economic evaluation will influence budgets
- Silo mentality at subsocietal level – not compatible with societal perspective ⇒ CE more appropriate.
- Budgetary impact and CE criteria can be combined (Sendi, Nuijten) “Cost-effectiveness affordability curves”.

Threshold

- League tables (Eichler)
 - Listing according to CE ratio
 - Select until budget is reached
 - Combines CE and budgetary constraints
 - BUT: ignores equity, which may lead to anomalies: allocation of inordinate share of available resources to some diseases, while leaving others untreated (Ham).

Threshold

	Cost-effectiveness	Budget		Affordable
	ICER (Euro/QALY)		Cumulative	
Program A	1000	5	5	
Program B	2000	6	11	
Program C	2500	1	12	
Program D	3000	22	34	
Program E	3500	2	36	35

ICER (Euro/QALY)				threshold	measure
(2004 US\$)					
Institutions	US		93,500.00		QALY
	Canada		17,600.00		QALY
	WHO			3 x GDP/capita	
	US	dialysis	108,600.00		DALY
	Japan		74,700.00		DALY
	Canada		74,400.00		DALY
	France		73,200.00		DALY
	Germany		70,200.00		DALY
	UK		66,400.00		DALY
	WTP	Human capital		24,777.00	
Contingent valuation			161,305.00		DALY
Revealed preference/job risk			428,286.00		DALY
Revealed preference/nonoccupation			161,305.00		DALY
Revealed preference WTP			165,600.00		LYG
Other programs	residential	US	43,600.00		LYG
	transportation	US	67,900.00		LYG
	occupational	US	424,300.00		LYG
	environmental	US	5,091,900.00		LYG
	toxin control	Sweden	23,800.00		LYG
	road accident prevention	UK	48,128.00		LYG
					LYG
Retrospective Towse	(n=41 cases)	UK	20-30000		QALY

Threshold

Issues

- Thresholds are historically set without justification
- Thresholds never have been upgraded for inflation
- Who decides on threshold?
- Comparability:
 - Health economic community: QALY
 - WHO – World Bank: DALY
- Thresholds differ substantially between countries
- Society perspective, but other thresholds in other sectors
- Unequal access patients in Europe only due threshold

RELEVANCE COST/QALY DATA

Relevance of Cost/QALY Data

Do the standard practices of Economic Evaluation have an impact on health solutions to current health problems?



New reality

Aging
Chronic diseases (cancer?)
Genetics
Small targeted markets
etc.

New solutions

Biotechnologies
High production price
Specialized prescribers
etc.

Relevance of Cost/QALY Data

Some ultra-orphan drugs in current use by the NHS

Product	Condition	Prevalence	Preliminary estimated ICER (£ per QALY)
Agalsidase beta (Fabrazyme)	Fabry's	200	203,009
Imiglucerase (Ceredase)	Gaucher's (types I and III)	270	391,244
Laronidase (Aldurazyme)	Mucopolysaccharidosis (type 1)	130	334,880
Miglustat (Zavesca)	Gaucher's (type I)	270	116,800
Nonacog alfa (BeneFIX)	Haemophilia B	350	172,500
Iloprost (Ventavis)	Primary pulmonary hypertension	100	23,324

Relevance of Cost/QALY Data

Selected C-E ratios for technologies recently covered by Medicare

- Left-ventricular assist devices: \$ 500,000 - \$ 1,4 million / QALY
- Implantable cardioverter defibrillators: \$ 30,000 - \$ 85,000 / QALY
- Lung-volume reduction surgery: \$ 100,000 - \$ 330,000 / QALY
- PET for Alzheimer's disease (over \$ 500,000 / QALY)

Relevance of Cost/QALY Data

NHS decision to pay for cost-ineffective treatment is not necessary irrational

- It relies on some implicit form of social preferences
- Is it evidence-based when just deciding on cost-effective treatments?
- These alternatives may nevertheless be “*efficient*” in the sense they maximize a Social Welfare Function (SWF) under a budgetary constraint
- CE is not an end by itself

Relevance of Cost/QALY Data

Ongoing activities

- €80,000 per QALY as a maximum is mentioned in an advisory report to the Dutch government
- No official status for policy
- The committee was not expert on the topic and did not mention the methodology of QALY and € / QALY assessment
- Suggestion is to combine the willingness to pay with burden of disease



Relevance of Cost/QALY Data

...

Relevance of Cost/QALY Data

Evolution of thresholds in future ?

- Published opinions expressed by economists and policymakers are split
- Eichler et al. ¹ think that CE thresholds will gradually become a reality
 - Consistency question
 - Transparency question
 - Maybe move from implicit to more explicit threshold (?) – predictable decision rule
- CE is and will not be the only decision criterion
 - Equity
 - Preferences
 - Budget Impact
 - “Rule of rescue”

Relevance of Cost/QALY Data

Evolution of thresholds in future ? (continued)

- Countries are getting richer and richer, whereas the threshold (willingness-to-pay per QALY) has a decreasing trend
 - NICE statements
 - Health Economists opinions
 - Non-inflation adjusted thresholds from old publications – hence real decreasing
 - UK university research

BROADER PERSPECTIVE

Broader perspective

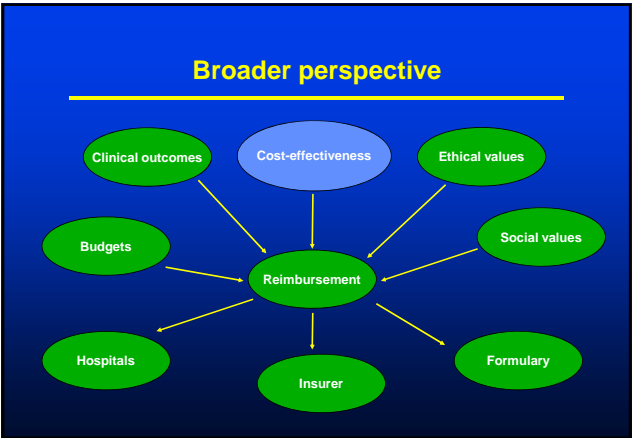
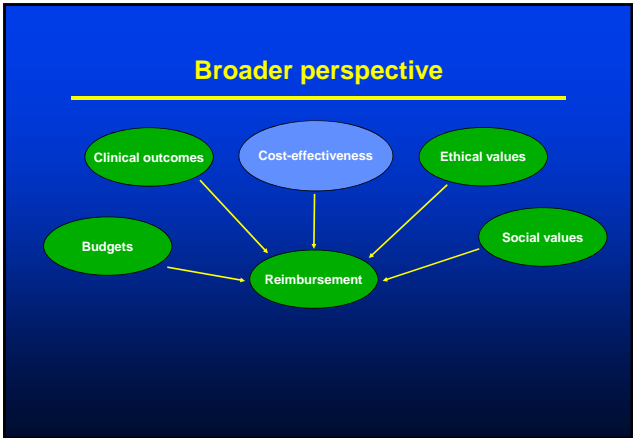
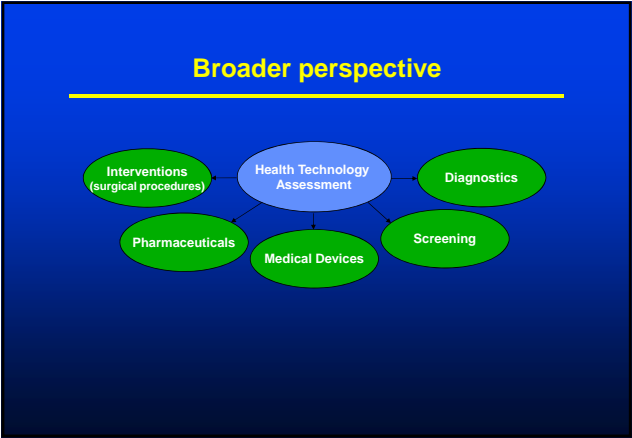
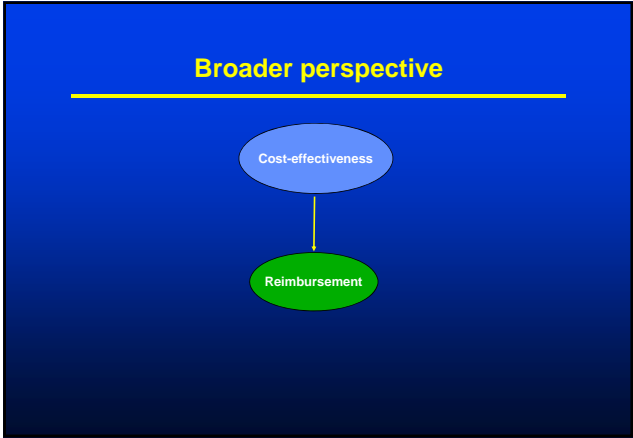
Inconsistencies ICER vs. reimbursement decision

		Cost-effectiveness	
		YES	NO
Reimbursement	YES		lung transplant
	NO	Viagra	

Broader perspective

Central vs. decentral authorities

- Mismatch between NICE's threshold and other health care decision makers
 - > Primary care trust: Cancer - 19,000 ; circulatory 12,000
 - > NHS: 20,000-30,000
- What determines threshold? ➡
 - > Society's WTP
 - > Size of budget
 - > Level of health care inflation
 - > Discount rates



Broader perspective

Need for consideration social values:

- Williams (94), Nord (99): favour consideration of social values.
- Williams (06): HTA community “cannot seem to get out of the starting blocks when it comes to considering objectives outside of efficiency. Great unmet need in doing so.

Innovation

Inclusion social values in appraisal process:

- Australia: Separate budget for life saving drugs, which are not cost-effective.
- UK): end-of-life treatment.
When such treatments have an incremental cost effectiveness ratio (ICER) in excess of the upper end of the range normally approved

Broader perspective

Criteria

- Regulatory data: medical information on efficacy and
 - Cost-effectiveness data: guidelines
- ↓
- Social and ethical values ?
- ↓
- No systematic set of principle
 - No process of assessment
 - Included in HTA ?

Broader perspective

Inclusion social values in appraisal process:

- Australia (2006): Separate budget for life saving drugs, which are not cost-effective.
- UK (2005): set of recommendations:
 - Orphan drugs: Pay premium for drugs to treat patients with very rare diseases - prevalence < 1/50,000
 - Approach and use of economic evaluations
 - Guidance on judgements that should be applied to social values - no formal guidelines

Broader perspective

Orphan drugs:

- Review of five markets (incl. Europe, US, Japan):
 - Drug price: 10 time shigher
 - ICER: GBP 23,000 to 390,000 / QALY
- ↓
- 35% of countries half of drugs aavailable
- ↓
- Other values considered than cost-effectiveness ?

Broader perspective

Orphan drugs: ROI

- Few number of potential patients
 - Fixed cost of R&D
 - No economies of scale
 - ROI only with premium price
 - Cost/QALY > threshold ⇒ No reimbursement
- Question: fair ?
- Patient ? Having rare disease – no treatment due to ICER
 - Pharma ? Priority medince program faciliates registration, BUT not reimbursement

Broader perspective

Orphan drugs: different asesment

- (Drummond 2007): include social values
 - Do standard HTA methods adequately reflect societal preferences?
 - How are those societal preferences measured?
 - How are these societal preferences used to determine priorities for scare resources?

Broader perspective

End-of-life drugs: different assessment

- ICER exceeds GBP 30,000
- Criteria:
 - LE < 24 months
 - Extension of life by 3 months
 - Small populations

Broader perspective

Questions:

- What is meant by societal values?
- Consider patient related (e.g. age) versus population related (e.g. rule-of-rescue).
- How have/might they be measured, elicited and assessed?
- What would be fair process of selecting values to include in HTA?
- How might these values vary in relevance in different situations?
- Which values should be included in HTA?
- How have/might social values are included in HTA along with cost-effectiveness?

ALTERNATIVES

Alternatives

Thresholds and weighting

- Cost-effectiveness: What should be threshold for ICR ?
- =Euro 20,000 ?
- What should be thresholds for other criteria ?
 - Patient satisfaction
 - Ease of use
 - Safety
- What should be weight of all criteria in overall decision?

Alternatives

- What should be thresholds for other criteria ?
 - Patient satisfaction
 - Equity
- What should be weight of all criteria in overall decision?
- Who decides on weight of all criteria?

Alternatives

Value of statistical life (Seeverens)

- The valuation of a change of risk rather than the valuation of a specific individual
- Fatality risk reduction 1:100,000 (one death per 100,000 people per year) can be given an economic value
- Makes comparison to societal sectors outside health care possible, but quality of life lost as outcome parameter

WHAT IS THE ROLE OF COST-EFFECTIVENESS DATA IN THERAPEUTIC INNOVATION AND INEQUALITIES OF HEALTH CARE?

ISPOR 9rd Annual European Congress

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THRESHOLD

ICER (Euro/QALY)			
(2004 US\$)			
		threshold	measure
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Threshold

Issues

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- Thresholds never have been upgraded for inflation
- Who decides on threshold?
- Thresholds differ substantially between countries
- Society perspective, but other thresholds in other sectors
- Unequal access patients in Europe only due threshold

Innovation

ICER as final decision criterion:

- After reimbursement: additional clinical data show much more clinical benefit than registration data
⇒ positive impact on disease progression ⇒
Cost/QALY < threshold



Conclusion:

- ICER based on registration data may underestimate true cost-effectiveness of innovation !
- Innovative products need a chance to prove themselves in real life ?

Innovation

CE-assessment of innovative drugs requires more time than “standard” new drugs.

- Limited data was available at time of launch
- No experience for physicians and patients with biologicals in daily practice

Learning curve effect

Underestimation of ICER at time of launch

Inappropriate rejection for reimbursement

CONCLUSION

Broader perspective

Criteria

- Regulatory data: medical information on efficacy and
- Cost-effectiveness data: guidelines

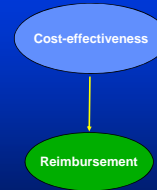


- Social and ethical values ?

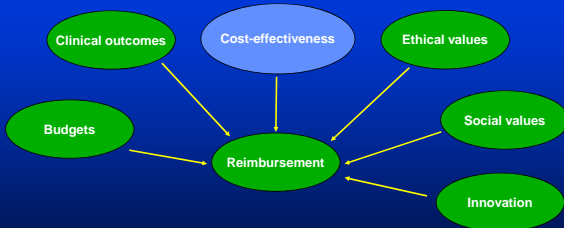


- > No systematic set of principle
- > No process of assessment

Broader perspective



Broader perspective



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