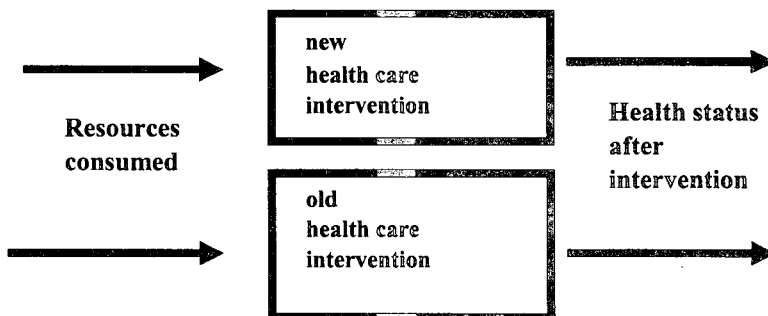# 경제성 평가 방법론
-연구설계와 결과평가-

**Economic evaluation:
study design and outcome evaluation**

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Economic Evaluation

Resources
consumed

→

| new |
| health care |
| intervention |

→ Health status
after
intervention

| old |
| health care |
| intervention |

→

Question:

Does the improved health status justify the
additional resources required for the new
intervention as compared to the old intervention?

Trends in economic evaluation

Decade	approach	cost	outcome
60's	cost-benefit analysis	$	$
70/80's	cost-effectiveness analysis	$	natural unit
80/90's	cost-utility analysis	$	QALY
00's	outcome measurement: utilities, conjoint analysis, willingness to pay	$	QALY or $ (WTP)

Phases in an economic evaluation

Phase 1: design of the study

Phase 2: measuring and valuing costs

Phase 3: measuring and valuing benefits

Phase 4: discounting

Phase 5: sensitivity analysis
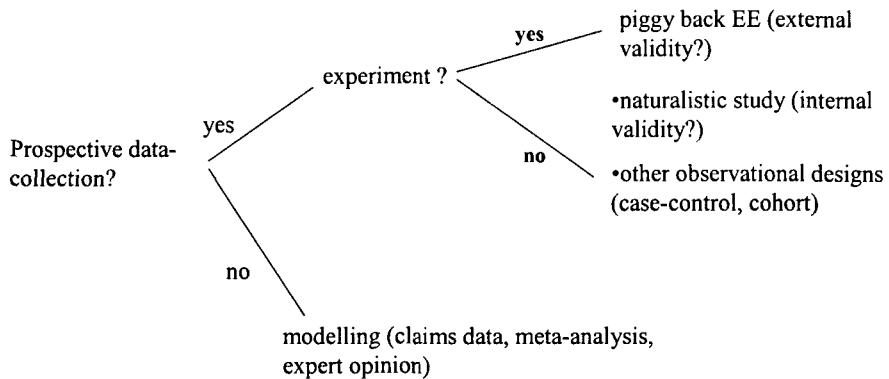
Phase 6: applying a decision rule

Phase 1:design of the study

- perspective (societal/third party payer)
- selecting the alternative
- experiment / model
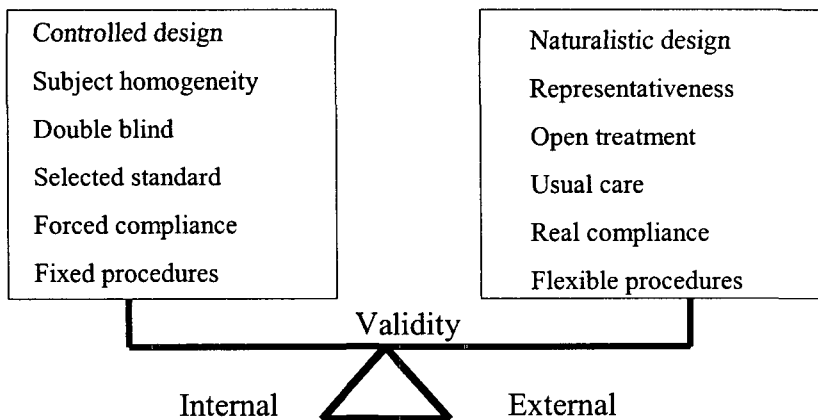- outcome parameters
- time horizon

Choice of comparator

- most efficient alternative
- standard treatment (volume, market share)
- consider "no treatment"

Design of the study

piggy back EE (external validity?)

yes

experiment ?

yes

no •naturalistic study (internal validity?)

•other observational designs (case-control, cohort)

Prospective data-collection?

no

modelling (claims data, meta-analysis, expert opinion)

The design determines the extent of generalisability

Controlled design
Subject homogeneity
Double blind
Selected standard
Forced compliance
Fixed procedures

Naturalistic design
Representativeness
Open treatment
Usual care
Real compliance
Flexible procedures

Validity

Internal   External

Modelling complementary to prospective approach

- intermediate to final outcome

- beyond trial duration

- beyond indications trial patients

- beyond trial setting (costs and outcomes)

- compliance patients and physicians

Time Horizon

- choose time horizon
  - all consequences in terms of costs and outcomes are taken into account
- if observation period of a clinical trial is shorter
  - modelling may be appropriate to study long term consequences

Principles of costing : (phase 2)

- Resource use by all parties concerned (societal perspective)
- Actual use of resources, which can not deployed elsewhere
- Financing system is irrelevant

- identification of resource items
- measurement of resource use
- estimation of the value of the resources

Phase 3: outcome

- dependent on relevant outcomes
- CEA: Natural units
- CUA: QALY
- CBA: monetary valuation

Outcome measures

- CEA and CUA
  - CEA: single, program-specific, unvalued, natural units
  - CUA: single or multiple, general, valued
- CBA
  - value benefits in monetary terms : worthwhile?
  - benefit : not only cost savings
  - but also monetary value of health outcome

Outcome measures 1: CEA

- Choice of effectiveness measure
  - final output. life-years gained
  - intermediate output : cases found, patients treated.
- admissible intermediate output
  - link between intermediate and final output
  - some values in itself. diagnosis. provide reassurance.
- Effectiveness data : How should be obtained?
  - availability of data: crucial
  - major source: medical literature
  - quality, relevance

Outcome measures 1: CEA

- data from published literature
  - single trial
  - overview or meta-analysis
- Relevance
  - Methodologic principles
  - literature search techniques, inclusion/exclusion criteria, choice of endpoint, patients characteristics, details about therapy(drug dose), statistical procedures, sensitivity analysis

Outcome measures 1: CEA

- Quality
- Level of evidence
  - Level I   large randomized trials with clear-cut results   Grade A
  - Level II   small randomized trials with uncertain results   Grade B
  - Level III non-randomized, contemporaneous controls   Grade C
  - Level IV   non-randomized, historical controls   Grade D
  - Level V   no controls, case series only   Grade E

Modelling vs. empirical research

- Empirical research: to gather data and information
  - prospective trials, retrospective data gathering (patient files, administrative databases).
- Modelling: to synthesise data and available information
- 'Models provide an explicit bridge between primary data and the decision they inform'

Modeling: Why

- To extend available information:
  - to extrapolate trial results from a short term to a longer term
  - to add cost data to outcome trials
- To combine available information:
  - to extrapolate intermediate results to final results
  - to combine alternative courses of action
- To generalise trial results
  - from controlled trial circumstances to daily practice
  - from (academic) trial setting to daily (general hospital) setting
- To explore potential value of empirical research
  - to estimate the value of empirical research
  - to generate research hypotheses
  - to identify crucial information and data

Decision analytic modelling

- Comparison of two or more diagnostic and/or therapeutic strategies
- The consequences of the alternative courses of action are uncertain
  - different clinical events (success, failure, complications etc.) might occur
  - several final health outcomes are possible
  - different costs can be relevant
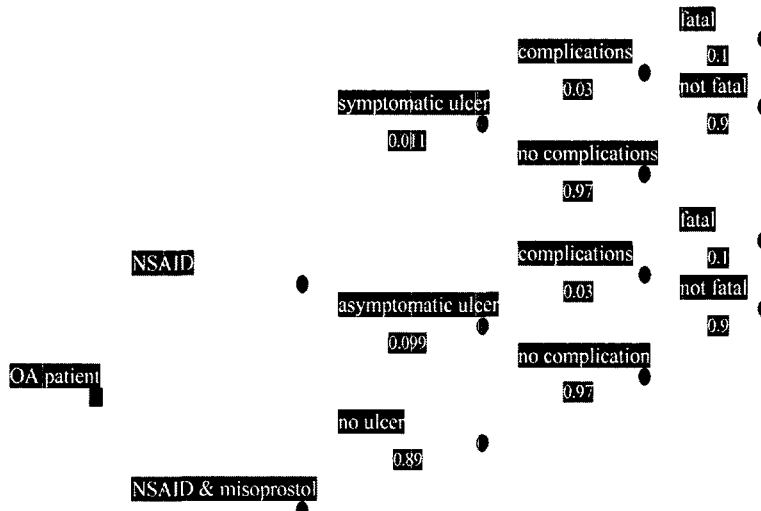- A patient population can be defined that might benefit

Structure of a decision analytic model

- Definition of the patient 'population'
- Comparison of alternative strategies
- Definition of probabilities of (clinical) events and related costs
- Patient health state defined as final endpoint as a result of a clinical pathway

Results of a decision analytic model

- Probabilities to reach a health state (path probabilities)
- Path probability * pay off (costs, health state): contribution to the overal, expected value of a strategy
- Expected value (costs, health state) of the diagnostic/therapeutic strategies compared
- Comparison of the diagnostic/therapeutic strategies on the basis of the incremental cost–effectiveness

Example decision tree

OA patient

NSAID

NSAID & misoprostol

symptomatic ulcer
0.011

asymptomatic ulcer
0.099

no ulcer
0.89

complications
0.03

no complications
0.97

complications
0.03

no complication
0.97

fatal
0.1

not fatal
0.9

fatal
0.1

not fatal
0.9

Markov modelling

- A patient's situation may vary over time
- The states that can be distinghuised are different regarding costs and value of health

Questions and answers:
- What is the duration that a patient will be in the specific health states
- What is the total value (costs, health) of the patient's time in the different health states

Markov structure
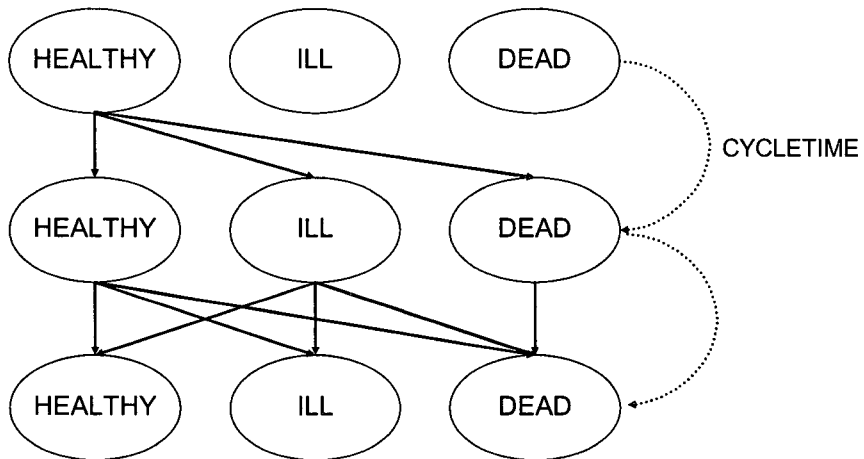
Modelling con's

- Does not result in new data or new information
- (Over)simplifies the complicated, real world
- Model structure subject to bias
- Model input subject to bias
- Misinterpretation of the results is easy

Modelling pro's

- Makes explicit definition of relevant patient group, clinical events, patient outcome, costs etc. necessary
- Shows what data and information are lacking
- Shows uncertainty of input and outcome
- Makes it possible to examine the impact of input uncertainty
- Relatively fast and simple (compared to empirical research)
- Relatively cheap

Outcome measures 2: CUA

- Why CUA?
  - to compare a broad set of interventions
    different interventions: different effects
  - to incorporate a large number of outcomes
    life extension, quality changes, side effects
  - to weight the different outcomes
    important: more valued
    consumer preference

Outcome measures 2: CUA

- By converting effectiveness data to a common unit of measure, like QALYs gained
- changes both in the quality of life (morbidity) and in the quantity of life (mortality)
- simultaneously incorporated in the analysis
- In the QALY approach, the quality adjustment is based on a set of values or weights called utilities, *one for each possible health state*, that reflect the relative desirability of the health state.
- The conventional scale for utilities is death = 0 and perfect health or full health = 1

CUA : when ?

- Health-related quality of life is an important outcome
- A health care programme affects both morbidity and mortality
- To compare programmes that have a wide range of different kinds of outcomes (resource allocation decisions)
- To compare with programmes evaluated by CUA in the past

CUA: Example

Treatment programme A
- Average costs: € 20,000
- Utility for health state during tr eatment of 6 months is 0.6
- After treatment half of the pati ents die
- Other half of the patients live on average for 3.5 years
- In a health state with a utility o f 0.8

QALYs = (0.5*0.6)+(0.5*3.5*0.8) =1.7

Treatment programme B
- Average costs: € 30,000
- Utility for health state during tr eatment of 6 months is 0.5
- After treatment 40% of the pati ents die
- Other 60% of the patients live on average for 4 years
- In a health state with a utility o f 0.8

QALYs=(0.5*0.5)+(0.6*4*0.8)=2. 17

Incremental Cost-Utility ratio is 10,000/0.47 = € 21,277

Health Related Quality of Life (HRQoL)

- Subjective
- The patient reports (not the doctor)
- a multi-dimensional construct Dimensions:
  - Physical well-being
  - Social well-being
  - Emotional well-being
  - Usual activities (Self care, Housekeeping and Paid and unpai d work)
  - Pain
  - Symptoms

Quality of life instruments

- Generic:
  - EuroQol instrument EQ-5D
  - Health Utility Index
  - Quality of Well-Being
  - SF-36
  - Nottingham Health Profile
  - Sickness Impact Profile

- Disease / Condition Specific:
  - Developed for a specific disease s (Parkinson disease) or group of conditions (Cancer)
  - Contain detailed questions on di mensions of health that are affec ted by the disease concerned an d its treatment

Result of completing a quality of life instrument

- Description of a persons health state
  - Profile scores for every dimension
  - Summary scores
- Use in economic evaluation:
  - preference scores or utilities, reflecting the desirability of health states

Example: SF-36 profile scores

	Norm (adults U.S.)	Asthma
Physical Health	50	
Physical Functioning (3)	84.2	61
Role-Physical (4)	80.9	53
Bodily pain (7, 8)	75.2	77
General health (1, 11)	71.9	55
Mental Health	50	
Vitality (9a,e,g,i)	60.9	54
Social Functioning (6, 10)	83.3	80
Role-Emotional (5)	81.3	79
Mental Health (9b,c,d,f,h)	74.7	78

EQ-5D

Mobility
    I have no problems in walking about   ☐1
    I have some problems in walking about   ☐2
    I am confined to bed   ☐3

Self-Care
    I have no problems with self-care   ☐1
    I have some problems washing or dressing myself   ☐2
    I am unable to wash or dress myself   ☐3

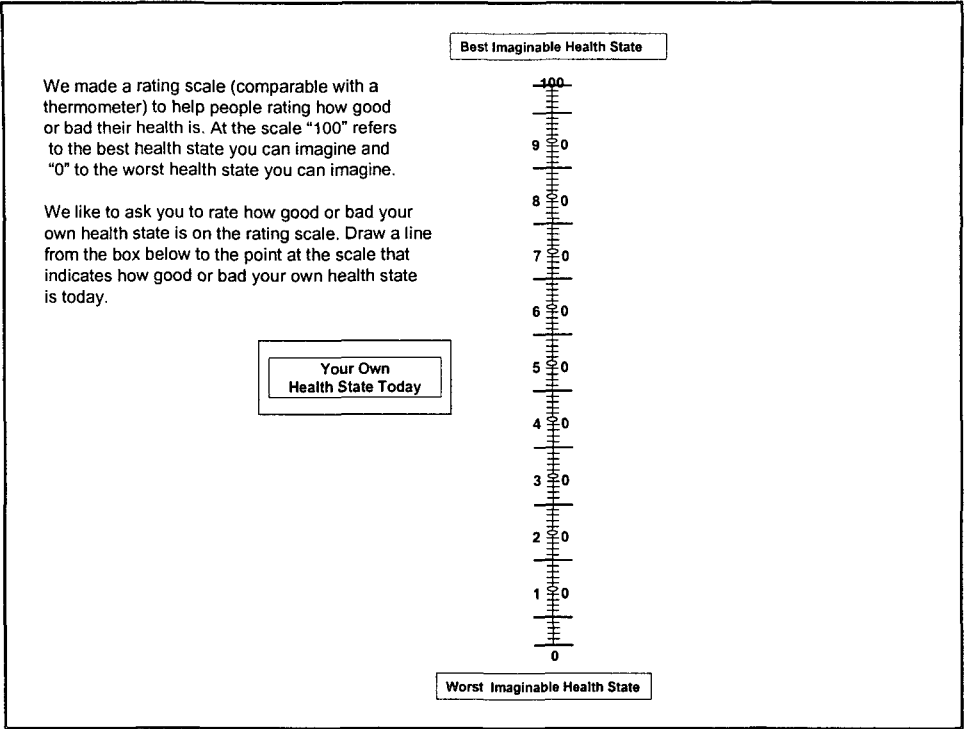Usual Activities *(e.g. work, study, housework, family or leisure activities)*
    I have no problems with performing my usual activities   ☐1
    I have some problems with performing my usual activities   ☐2
    I am unable to perform my usual activities   ☐3

Pain/Discomfort
    I have no pain or discomfort   ☐1
    I have moderate pain or discomfort   ☐2
    I have extreme pain or discomfort   ☐3

Anxiety/Depression
    I am not anxious or depressed   ☐1
    I am moderately anxious or depressed   ☐2
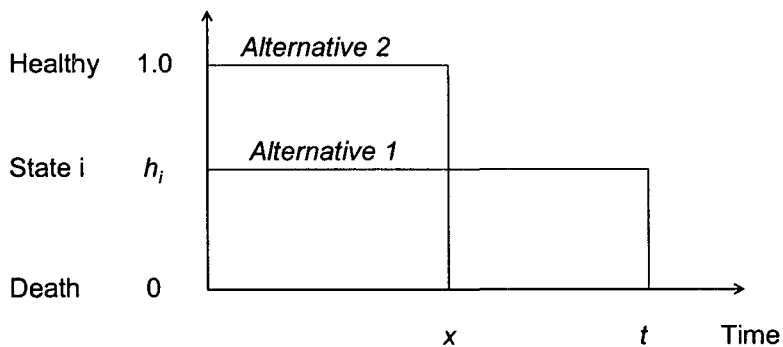   I am extremely anxious or depressed   ☐3

Slide 1

Best Imaginable Health State

We made a rating scale (comparable with a thermometer) to help people rating how good or bad their health is. At the scale "100" refers to the best health state you can imagine and "0" to the worst health state you can imagine.

We like to ask you to rate how good or bad your own health state is on the rating scale. Draw a line from the box below to the point at the scale that indicates how good or bad your own health state is today.

```
Your Own
Health State Today
```

100
9 0
8 0
7 0
6 0
5 0
4 0
3 0
2 0
1 0
0

Worst Imaginable Health State

Slide 2

How to assess the relative desirability (preference) of each possible health state?

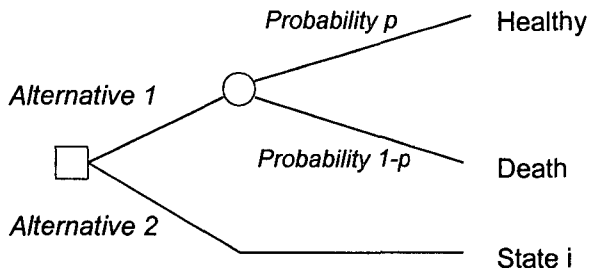| Response method	Question framing	
	Certainty (Values)	Uncertainty (Utilities)
Scaling	Visual Analogue Scale	
Choice	Time Trade-Off	Standard Gamble

QALY Analysis

- Value (V) of quality of life (Q)
  - $V(Q) = [0....1]$
    - 1 = healthy
    - 0 = dead
- Adjust life years (Y) for quality of life
  - QALY's = Y * V(Q)
    - Y: numbers of life years
    - Q: health state during life years
    - V(Q): the value of health state Q

Methods to value health state (TTO)

Healthy   1.0   *Alternative 2*

State i h_i *Alternative 1*

Death   0

     x   t   Time

Value for state i = h_i = x/t

Methods to value health state (SG)

Alternative 1

Probability p — Healthy

Probability 1-p — Death

Alternative 2

State i

Preference score (utility) for state i = h_i = p

Whose preferences count?

- Patients
  - Clinical QoL research
  - Medical decision making
- General Public
  - Economic Evaluation (resource allocation decisions)

Patients' values ≠ values of general public

- Patients
  - value their own health state
  - are familiar with the disease, its symptoms, the effects of treatment
  - adapt to the disease and treatment (coping),
  - resulting (in general) in higher values than the values of the general public
- Persons from the general public
  - are in general healthy people, only small fraction is sick
  - value hypothetical health states
  - resulting (in general) in lower values than the values of patients

Factors influencing the values of health state

- Valuation method
  - SG, TTO, VAS
  - whether or not in combination with the descriptive system of the health states to be valued
- Perspective
  - Patient
  - General public
- Operational definitions: Interview bias
- Country: Culture?
- Socio-economic factors:
  - Age, gender (hardly any influence)
  - Education (small influence)
  - Religion and beliefs about life after death

Outcome measures 3: CBA

- Decision making based on monetary value
  CEA/AUA: QALY league table
- Broader in scope. health and non-health
- Allocative efficiency
  CEA/AUA: production efficiency
- Quantify externalities(spill over effect)
  CEA/AUA: narrowly client-focused
  willingness-to-pay technique
- conforms more closely to Welfare Theory

Contingent valuation

- Appraches to the monetary valuation of health
  outcomes
  - human capital
  - revealed preferences
  - willingness-to-pay(contingent valuation)
- Asking individuals for their maximum
  willingness to pay (WTP) for a gain in health
- Fits in Cost Benefit analysis (CBA)

Example WTP question

- Are you prepared to pay ... for a drug that reduces the risk of getting a migraine attack by 50%?

Critique on CV-WTP

- WTP depends on ability to pay -> equitable?
- Scope effects: WTP responses tend to be undersensitive to the magnitude of benefit

- Budget constraint bias: WTP inflates valuations of interventi on asked about.
  When asked for an intervention in isolation, WTP is far in excess of WTP when intervention is considered in relation to other interventions

Application CV

- First: extensively used in transport and environmental economics
- More recently: in health economics
- Upward trend in health economics
  - 1985-90: 11 studies (Richard 2003);
  - 1991-96: 32;
  - 1997-02: 68

Fundamental for design

- No real market: researcher introduces a *hypothetical market*
- Distinction between saying and doing ->
  thus we prefer revealed preferences instead of stated preference
- If only stated preference possible, we prefer the next best: simulating a plausible real-life situation with sufficient possibility that respondents take it seriously

- Behavioural in design (not attitudinal only)
- A specific program with specific attributes

Key issues in design

- how is information presented?
- type of payment vehicle for WTP
- commodity valued under uncertainty?
- what time period for valuation?
- how survey administered?
- WTP or WTA?
- (questionnaire format)

WTP or WTA?

- WTP for a nice good/service (a benefit)
- WTA (= WT accept) for a loss, is the counterpart
- Systematically found: WTA > WTP, for the same good/service (not in line with welfare theory)
- Reason: the endowment effect

Phase 4: Discounting

- Principle:
  - Effects in terms of costs or health gains are weighted less when they occur later in time.

- Reasons:
- time preference
  - Impatience
  - diminishing marginal utility of income
  - uncertainty

- opportunity cost of capital
  - the existence of a positive rate of return implies that one resource unit in the future is valued less than one now!

Phase 5: uncertainty

- The values used in cost-effectiveness analysis are estimates
- Uncertainty is associated with all estimates
- Quantifying uncertainty through
  - Sensitivity analysis
  - Statistical analysis

Sensitivity vs. statistical analysis

- Sensitivity analysis
  - Quantifies uncertainty when values are:
    - Guessed
    - Determined from secondary sources
    - Approximated
- Statistical analysis
  - Quantifies uncertainty when values are estimated from a sample of a population such as in a randomised clinical trial

Types of Sensitivity analysis

- Goal is to find out how sensitive ICER is to changes in parameter.
- Univariate sensitivity analysis
  - vary only 1 parameter at the time
- Multivariate sensitivity analysis
  - vary 2, more or all parameters at the time
  - 'worst case' & 'best case'
  - threshold
  - Probabilistic
- Probabilistic sensitivity analysis

Univariate sensitivity analysis

- Change parameters one at a time, see how this influences ICER.
- Preferably change every parameter, if not feasible, at least identify key-parameters to change
- Example cholesterol lowering
  - mean survival is between 25.8 years and 26.2 years with 95% probability
  - then CER is between € 11488 and € 7658
  - If societal WTP is € 10,000
  - no clear recommendation is feasible.

Multivariate sensitivity analysis

- In 2-way analysis, two key parameters are varied
- Threshold analysis:
  - a decision maker defines a ICER above which a new treatment is unacceptable
  - assess which combinations of parameter estimates could cause the threshold to be exceeded
- 'Best case' and 'worst case' scenario give the most extreme outcomes of model.
  - If even in 'worst case' model outcome is acceptable, than we can be certain of outcome
  - If not, maybe not a problem, since likelihood of 'worst case' scenario might be far less then 2.5%

Problems

- How does one choose limits of range within which to vary parameter?
- When is the outcome considered sensitive to chan ges?

Choosing range

- If available use confidence interval (from RCT, case-control study or meta-analysis)
- Else use literature review, expert opinion, own judge ment
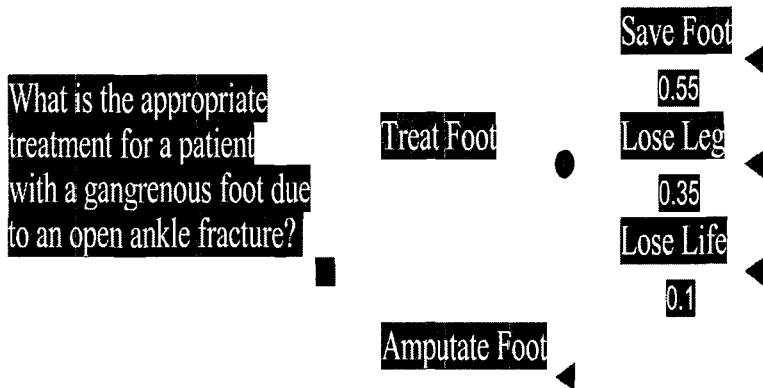- Always vary upwards and downwards (be critical whe n only one direction)

When sensitive?

- Easiest rule of thumb: when decision changes, i.e. IC ER is no longer acceptable if it was at point estimate, or becomes acceptable if it was not at point estimate

- Describe sensitivity in terms of relative sensitivity, i.e. results most sensitive for changes in A, B, C, and lea st for X, Y, Z

Probabilistic analysis

- Most informative method, since it presents extreme outcomes, but also likelihood of outcomes
- Define probability distribution for each variable
- Where possible, base distribution on trial data
- Draw random number from each distribution and calculate ICER
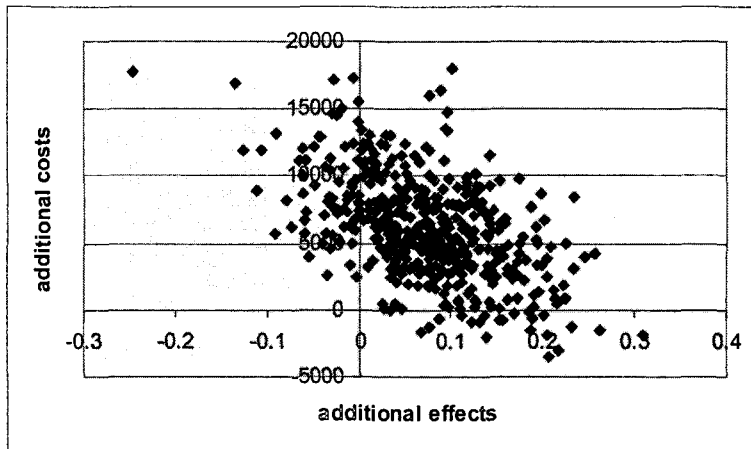- Repeat many times (1000–5000)

Example tree - utility

What is the appropriate treatment for a patient with a gangrenous foot due to an open ankle fracture?

Treat Foot

Save Foot
0.55

Lose Leg
0.35

Lose Life
0.1

Amputate Foot

Distributions probabilistic sensitivity analysis

Results :probabilistic analysis

Phase 6: Decision rule

Cost−effectiveness of strategy 2 versus strategy 1

$$\frac{cost\ (2) \quad - \quad costs\ (1)}{benefits\ (2) \quad - \quad benefits\ (1)}$$

- benefits in natural units (e.g. life years gained, healthy babies)
- benefits in QALY's

QALY league table

GM-CSF elderly with leukemia	$235,958
EPO in dialysis patients	$139,623
Lung transplantation	$100,957
End stage renal disease	$53,513
Heart transplantation	$46,775
Didronel in osteoporosis	$32,047
Statins in high cholesterol	
PTA with Stent	
terbinafine in onychomycosis	
Breast cancer screening	
Viagra	
Congenital anorectal malformation	
Totaal	

Dutch Experience: Priority setting

- Defining Basic health package
- Dunning criteria
  - Necessity
  - Effect
  - efficiency(cost-effectiveness)
  - individual responsibility