HEALTH ECONOMICS WORKSHOP

Seoul December 2005

Assessment of Healthcare Technologies: The Third Generation Tools

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How to Make Right Choices in Health?

A decision will be known as good one for Public Health if the difference between its advantages and its drawbacks in terms of population's health is strictly superior to the one that would have been observed had the decision not been taken.

Net gains in public health	=	Incremental population's health gains	-	Incremental population health losses subsequent to the additional investments

Implicit Health Sacrifices

An Unavoidable Dimension of the Choice in Favor of a Technology

- The advantages are measured in terms of efficacy Δ and quality of life Δ
- The drawbacks are measured in terms of risk differences and with the yardstick of the health actions that could have promoted and we have not been able to do considering what we have done … i.e. in costs

Benefit – Risks – Costs profiles
are at the heart of public health interest

- To make the concept operational, it is sufficient!!! to measure the realities it covers

Plan of the Intervention

- **EVIDENCE**
  - Evidence based medicine…
  - *Types of evidence and bias ?*
  - *How to move from experimental models to real life?*

- ***METRICS***
  - ***Measures of heath outcome***
  - *Why consider the cost?*
  - *What are the types of economic analysis?*

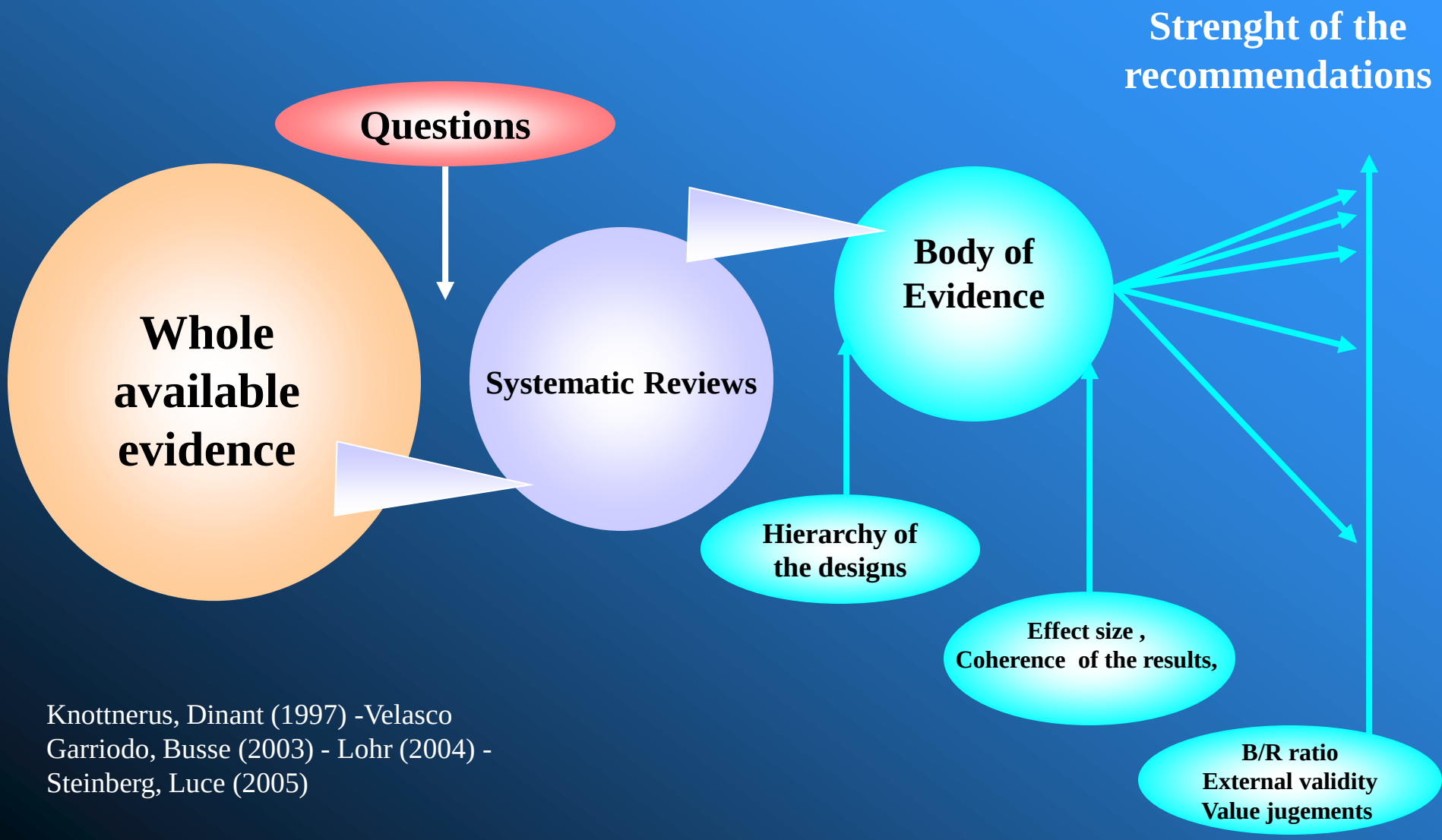
- ***ASSESSMENT CRITERIA***
  - *Decision criteria under CEA*
  - *Return on investment*
  - *Net public health benefit*

- ***HOW TO INFORM THE POLITICAL DECISION MAKING?***

THE EVIDENCE

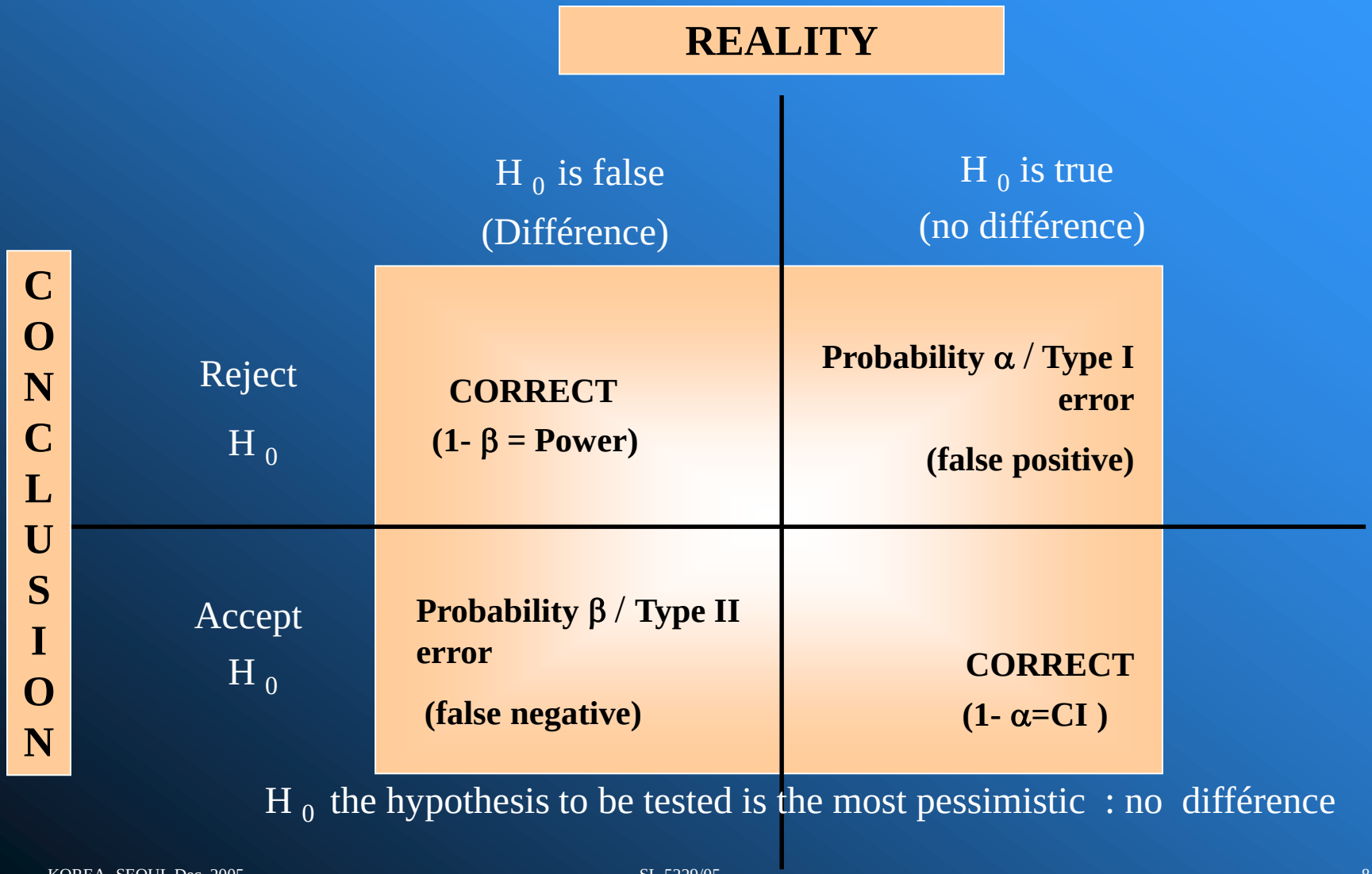
1) Evidence based Medecine…

Collecting and Weigthing the Evidence



Knottnerus, Dinant (1997) -Velasco Garriodo, Busse (2003) - Lohr (2004) - Steinberg, Luce (2005)

Threshold and Types of Errors



H_0 the hypothesis to be tested is the most pessimistic : no différence

Search For « Proof »

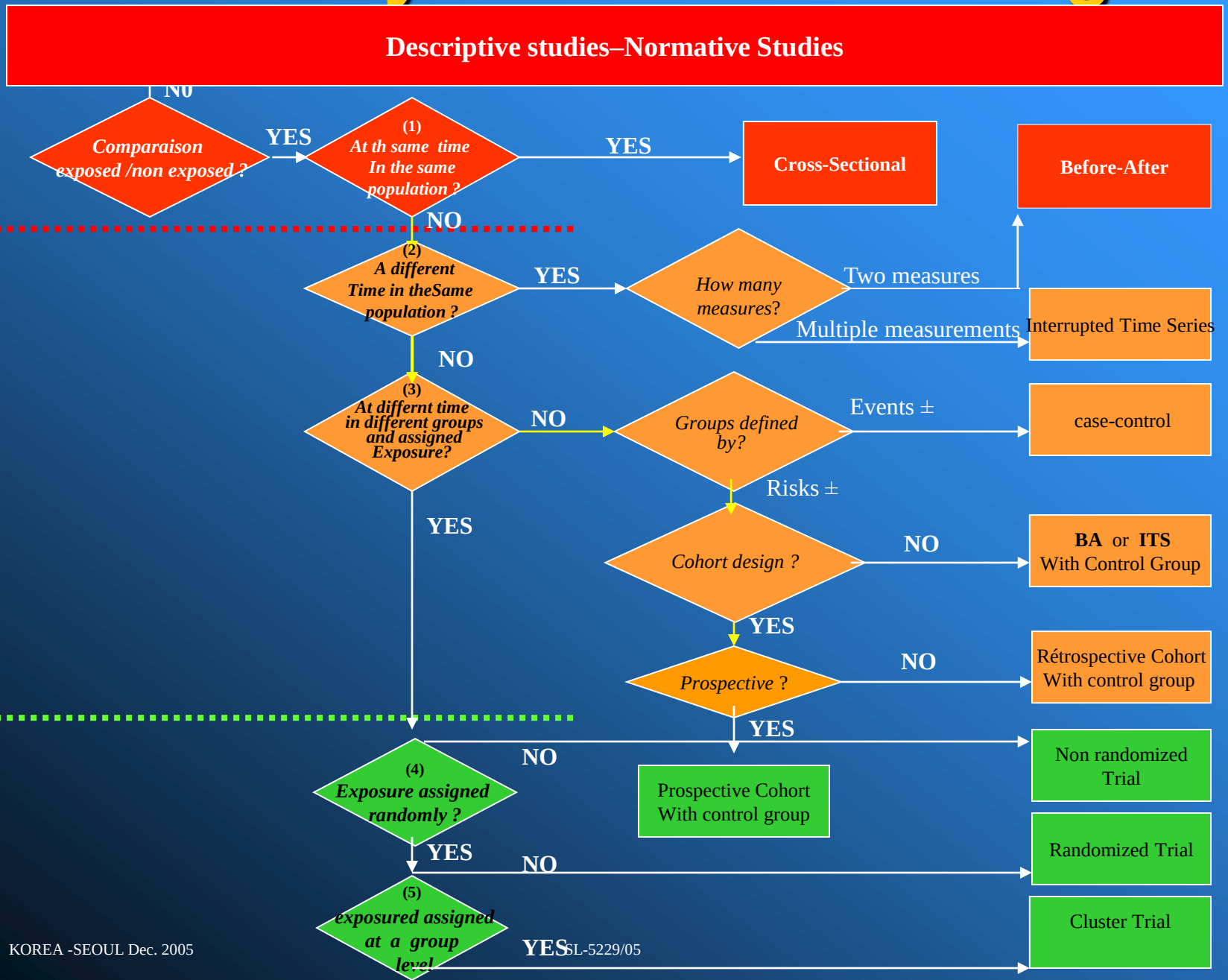
- Search for proof in the form of statistically significant results is a Common tendancy
- But « the absence of evidence is not the evidence of absence »
- Statistical significance does not specified the magnitude of an effect, or the comparison of benefits, harms and costs
- This approach should be avoided

Effect Size

- Absolute Risk (AR)
- Relative R (RR)
- Odds Ratio (OR)
- Number Necessary to Treat (NNT)

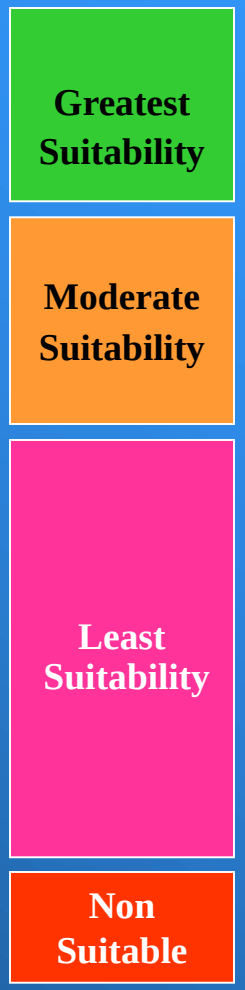
2) Types of Evidence and Bias…

Taxonomy of Reseach Designs



Hierarchy of Research Designs

- Randomised clinical trials, Non randomised trials
- Prospective et retrospective cohort
- Interrupted time series with comparison series
- Before-After study with control group
- Interrupted time series without comparison series
- Before-After study without control group
- Case Control study
- Cross sectional study
- Non comparative study: cases series,descriptive and normative study



The Ideal Study

- **Randomization** → ***Comparability of Populations***
  - Similar risk factor distribution
  - Not necessarily true in nature (e.g., new drug & new users)
- **Placebo arm** → ***Comparability of Effects***
  - External conditions that might affect rate should be similar
  - Not just the drug – also the management, etc.
- **Blinding** → ***Comparability of Information***
  - Avoid biased collection of information
  - Multiple levels: patient, doctor, assessor, analyst, etc.
- **But strong Selection Bias !**

The Limits of Randomized Trials

- Impossible direct comparison between all therapeutic options
- Truncated vision of the illness's evolutionary genius
- Negation of epidemiologic and institutional local realities
- Scotomisation of decisive elements for the decision-makers

(adverse events, QoL, pathways and contacts, any information other than those relating to the size of effects)

Risk of Bias in Observational Studies

Selection Bias

Case-mix

Regression to the Mean

Hawthorne Effect

Loss to Attrition

Measurement Error

New Technology

Secular Trends

Access

Seasonality

Maturation

Unit Cost Increases

Reimbursement

Benefit Design

Treatment Interference

3) How To Brige The Gap Between Experimental Model And Real Life ?

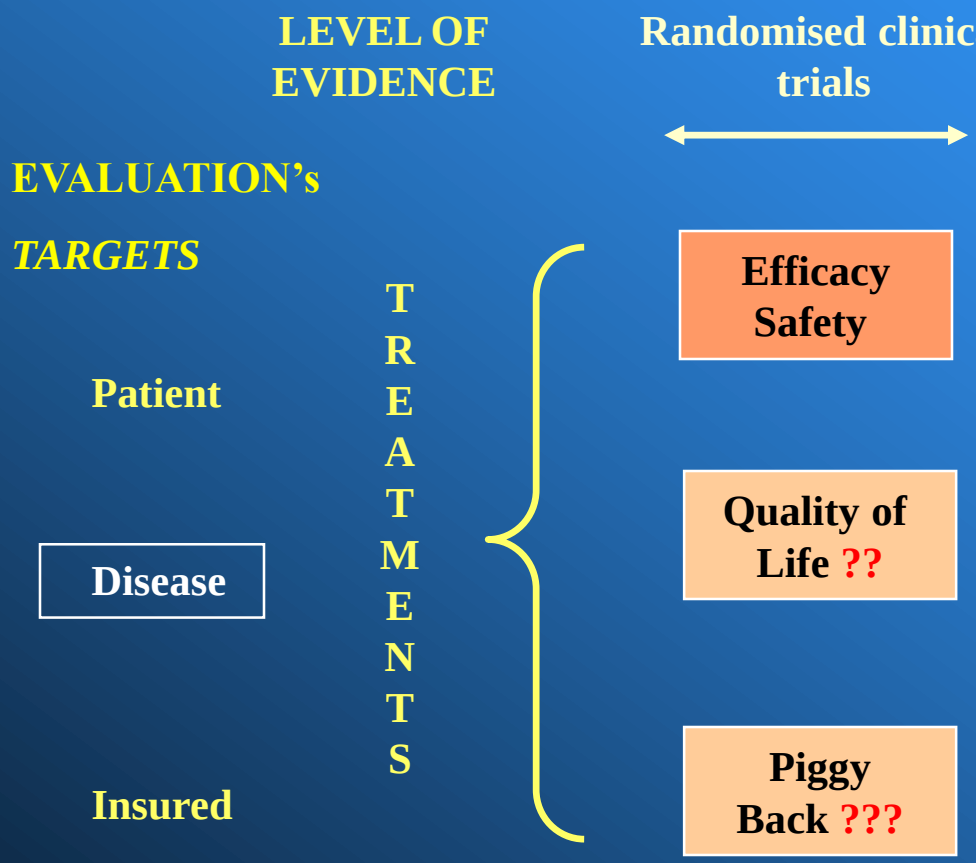
Who Should we Take Care of?

- The Patient?
- The Disease?
- The Insured?

Experimental Models and Real Life

- RCT are viewed as **the gold standard** for making comparisons between treatments.
- The question of interest in controlled clinical trials is **efficacy** « can the drug work in the **disease** for which it is intented to be used ? »
- In clinical practice the question is **effectiveness** « does the drug work in **patient** to whom it is offered **?** »

Experimental Models in Laboratory Conditions Prioritize The Disease

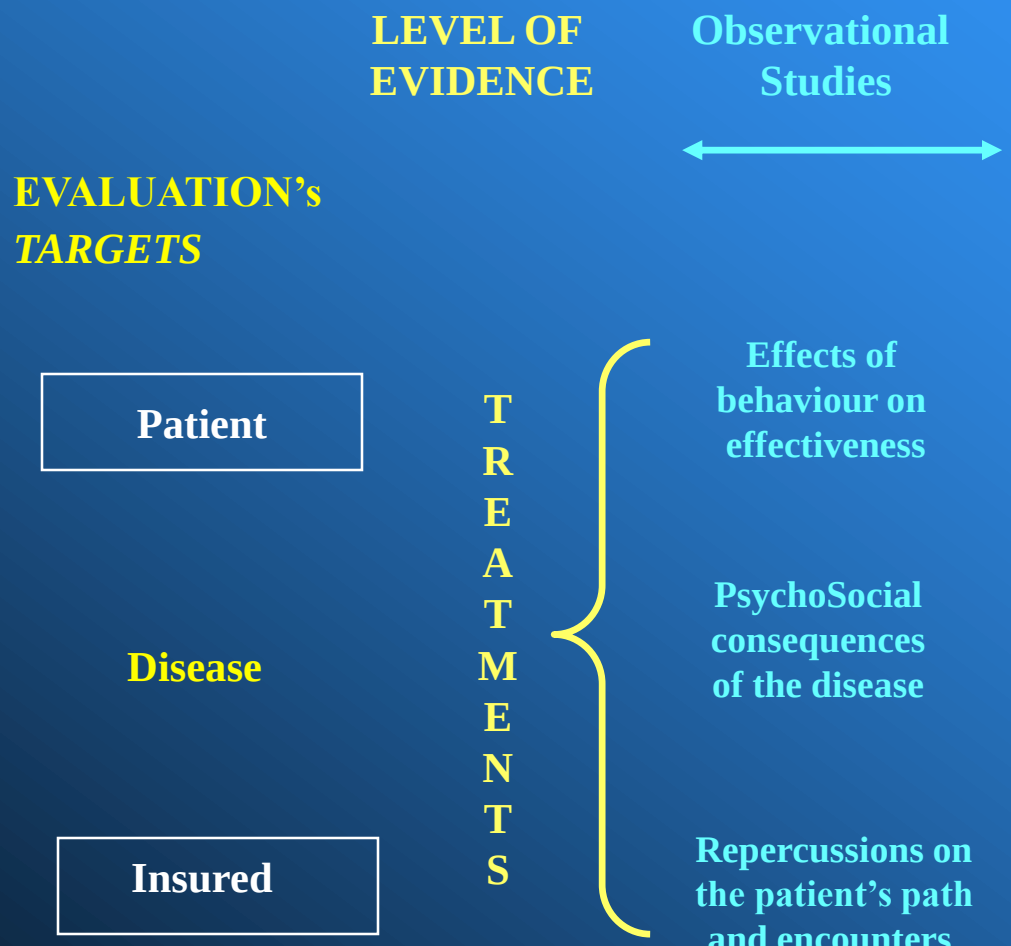


But The Results of RCT's are Limited in their Generalizibility

RCT are conducted under strict protocol-driven conditions with:

- **Well-defined homogeneous patient populations**
- **Restriction in co-morbid** conditions and concomitant medications
- **Short follow up**
- **Limited sample size**

Observational Studies Assess Impacts
of Individual's Behavioral Decision making Processes on Outcomes



But Without Control, They Only Show the Natural Course of Illness

- A study is called observational if everything is going on as it would have gone ***in the absence of the study***
- Observational study performed in clinical pratice provides information on how treatements are ***actually used*** by providers and patients when **individuals' decision making behavior can be observed** within a complex healh care systeme
- The lack of experimental plan increases the ***risk of selection bias*** due to no randomisation, causal inferences is not possible

How to Bridge the Gap Beetween Real Life and Experimental Models?

LEVEL OF EVIDENCE	Observational studies ⟷		Randomised clinical trials ⟷
EVALUATION's *TARGETS*			
Patient	TREATMENTS	Effects of behaviour on effectiveness	? Efficacy Safety
Disease		PsychoSocial consequences of the disease	? Quality of Life
Insured		Repercussions on the patient's path and encounters	? Piggy back

Bayesian Analysis: a New Approach To Synthesis

- Bayesian analysis focus not just on the question « what is the effect of a vs b » but « how this trial change your opinion about a vs b »
- The analyst is compelled to state the prior distribution excluding the evidence of the trial, the likelihood of different values based on the trial and to combine both sources to produce an overall synthesis
- Bayesian approach is thus an explicit quantitative use of external evidence in the interpretation of a study. It allows inference from observational data, experts views and values jugements

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- **METRICS**
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  - *Why consider the cost?*
  - *What are the types of economic analysis?*
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THE METRICS

1) Measures of Health Outcomes

Dichotomous Outcomes

- The most common
- Probability of outcome (risk)
  - In the treated group R_T
  - In the control group R_C

Evidence Table

- To summarized the evidence (tabulated datas)
  - For each study, a 2x2 table per outcome

Outcome 1	Event présent	Event absent	Size (number)
Treated group	--	--	--
Control group	--	--	--

Absolute Risk Différence (RD)

- $RD = R_T - R_C$

	Outcome	N	Risk probability
Grp T	45	180	45 / 180 = 0,25
Grp C	56	176	56 / 176 = 0,32

RD = 0,25 - 0,32 = - 0,07

- No effect RD = 0

Relative Risk (RR)

- $RR = R_T / R_C$

	Outcome	N	Risk probability
Grp T	45	180	45 / 180 = 0,25
Grp C	56	176	56 / 176 = 0,32

RR = 0,25 / 0,32 = 0,79

- Relative Risk Reduction

RRR = 1 – 0,79 = 21 %

Relative Risk, Interpretation

- RR < 1 $(R_T < R_C)$
  - the treatment decreases the relative risk of occurance of outcome
  - beneficial effect
- RR > 1 $(R_T > R_C)$
  - the treatment increases the relative risk of occurance of outcome
  - detrimental effect
- RR = 1 $(R_T = R_C)$
  - No Treatment effect

Odds Ratio

$$OR = \frac{R_T / (1 - R_T)}{R_C / (1 - R_C)}$$

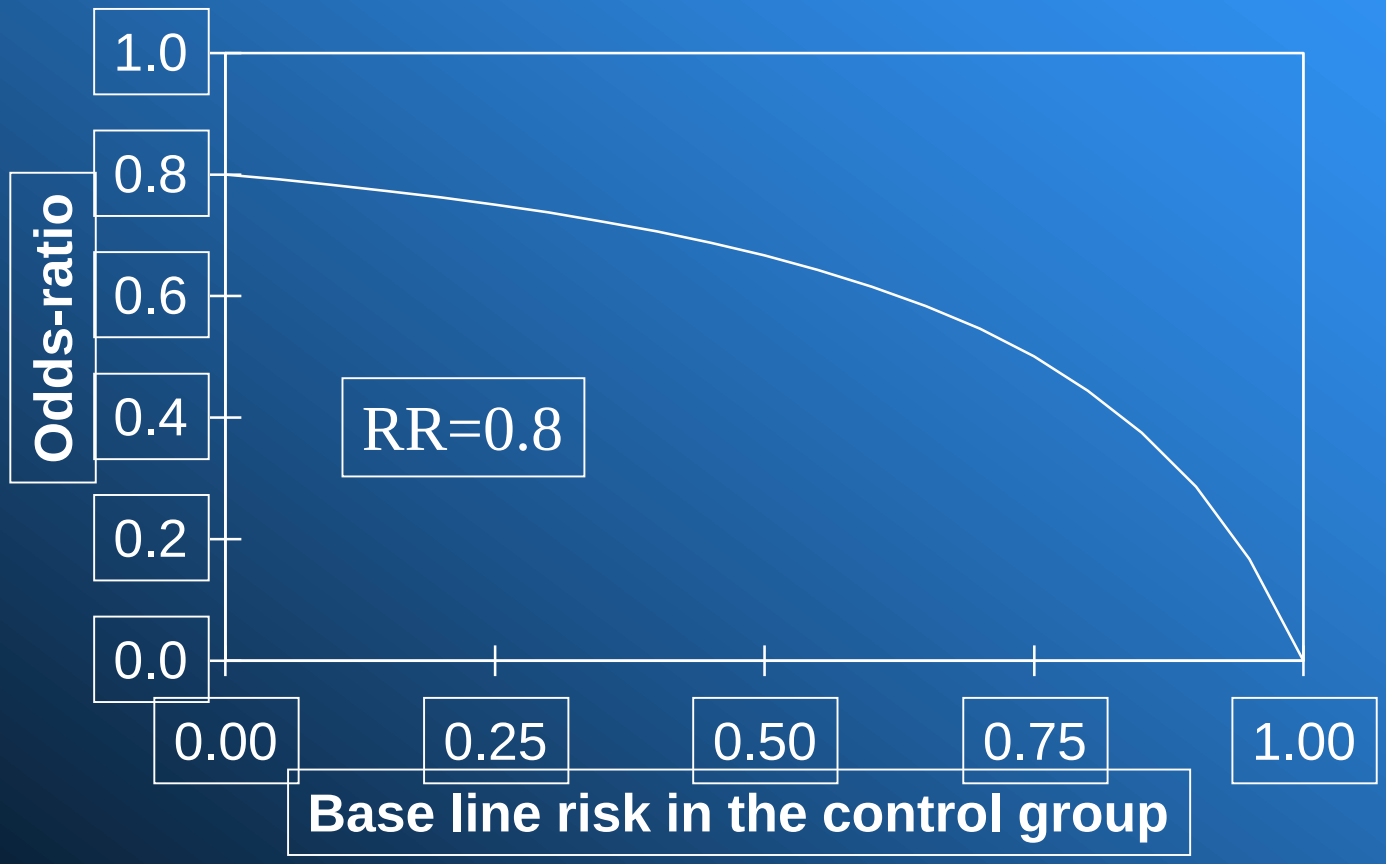
	Outcome	N	Risk probability
Grp T	45	180	45 / 180 = 0.25
Grp C	56	176	56 / 176 = 0.32

OR = (0.25/(1-0.25) /(0.32/(1-0.32)) = 0.71

- The odds ratio is an approximation the relative risk

Relation between RR et OR

OR is an approximation of the RR only when the base line is small (< 0,4)



Number Needed to Treat (NNT)

- NNT = Nb of patients necessary to treat to avoid an event
- NNT = 1 / RD

  1 / 0.07 = 14
- Interest
  - Ease of interpretation
- Limits
  - Problematic construction of the confidence interval

2) Why Consider Costs ?

The Economic Question

Where should we put our money to lighten the burden of illness?

Conventional treatment or innovative treatment**?**

The Answer

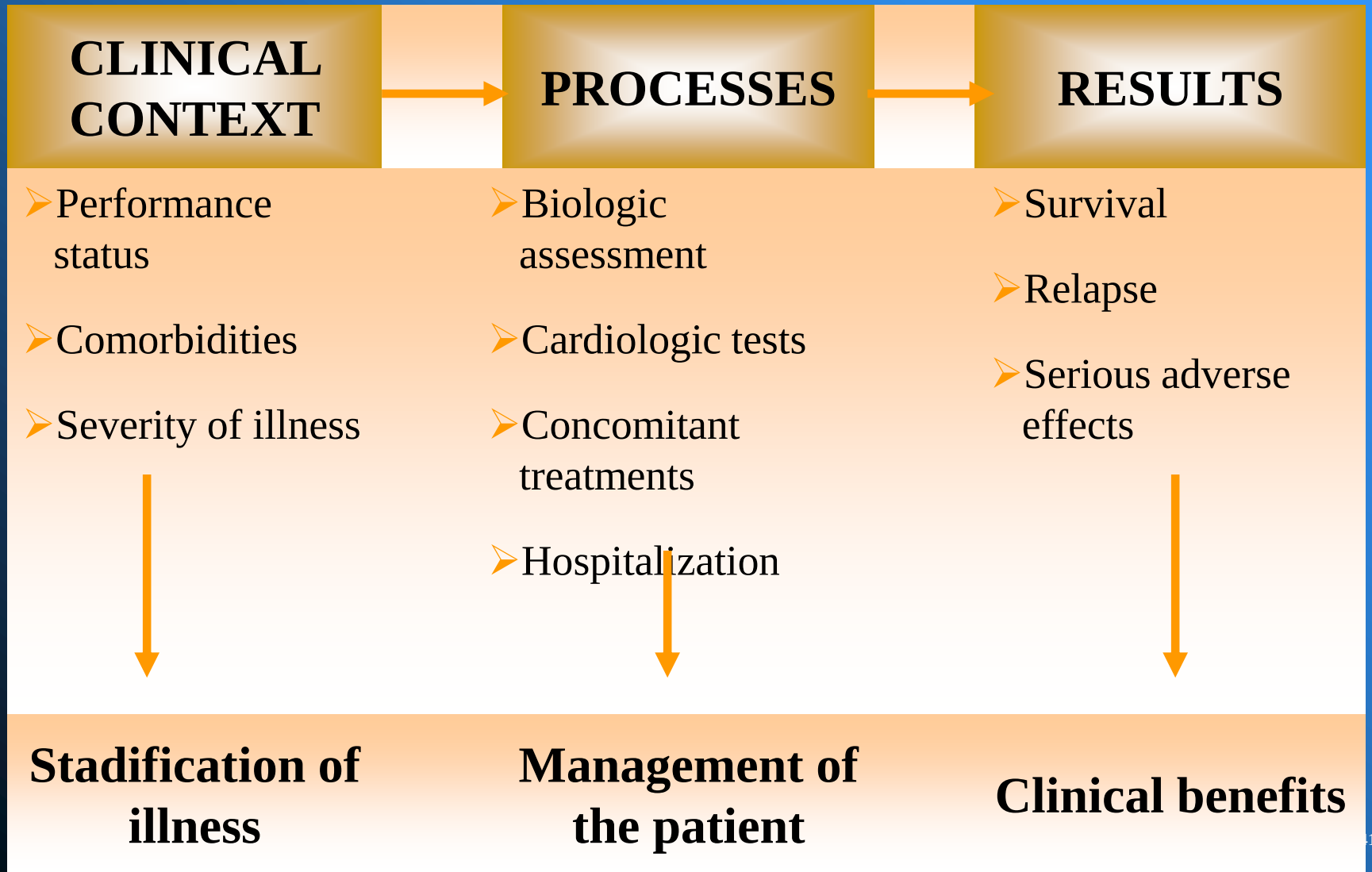
Choose the treatment which has the highest rate of return on the therapeutic, human and financial aspects per invested monetary unit.

Economic Analysis is a Subsdiary Downstream Discipline with respect to Medical Management

Economic assessment is to science what dental care is to medicine!

- It takes the footprints of clinical path
- It makes a mould of it
- It casts the mould with Euros

Clinical Parameters are Individual and Uncertain Data



Tariffs are Deterministic Variables

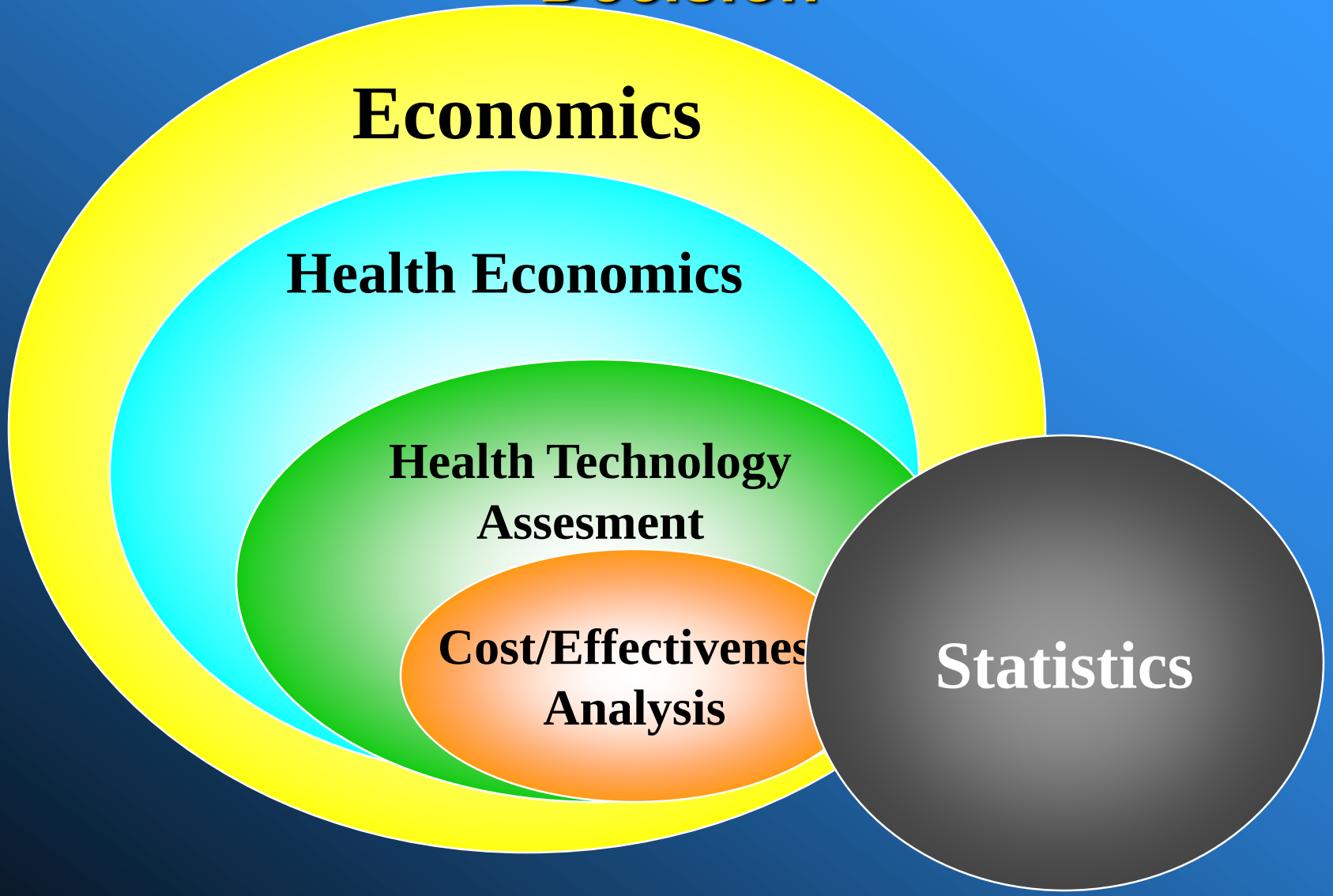
They are available off the shelves of the public libraries and not included in any case report form

Cost Categories

Inclusion and measurement will depend on the study's perspective and its time frame.

- Direct medical: medical care services
- Direct non-medical:
  - Patient time cost for treatment or intervention
  - Formal and informal caregiver time
  - Transportation
- Productivity (morbidity and mortality)
  - absenteeism
  - presenteeism

PhE: The Bridge Between Science and Decision



3) What Are the Types of Analysis in Economic Evaluation?

What are the types of analysis in Economic Evaluation?

- Cost Minimization Analysis (CMA)
- Cost Benefit Analysis (CBA)
- Cost Effectiveness Analysis (CEA)
- Cost Utility Analysis (CUA)
- Cost-of-Illness Analysis (COI)
- Budget Impact Analysis (BIA)

Cost-Minimization Analysis (CMA)

- When two or more interventions have been demonstrated to be equivalent in outcome or consequence, CMA is used to find the least expensive alternative.
- CMA is different from Cost Analysis, which chooses the least expensive alternative regardless of outcomes.

CMA (cont.)

- CMA is also different from “Efficacy Analysis” or “Effectiveness Analysis”, which focuses on “outcomes” only.
- Example: In-center vs. home hemodialysis in treatment End-Stage Renal Disease patients.

Cost-Benefit Analysis

- CBA is an evaluation method for comparing the monetary value of all resources consumed (costs) in providing a program or intervention with the monetary value of the outcome (benefit) from that program or intervention.
- In CBA, both costs and outcomes are measured in dollars.
- Advantage: CBA allows comparison of programs or interventions with entirely different outcomes.

CBA (cont.)

- If the interventions result in a stream of benefits and costs over time → Choose a discount rate and construct present value.
- CBA is difficult to perform because it requires that both costs and benefits be measured in (or converted into) monetary terms
  - Human Capital Approach
  - Willingness-to-Pay Approach
  - Conjoint Analysis
- $U(Y_a - CV, Z_{a1}) = U(Y_a, Z_a)$

Problems with CBA

- Result depends on dollar values assigned to life
- What about Quality of Life?

Cost Effectiveness Analysis (CEA)

- CEA is a method to determine which program or treatment accomplishes a given objective at the least cost.
- In CEA, the effectiveness is expressed in terms of non-monetary units that describes the desired objective.
  - lives saved (years of life saved)
  - disability days avoided
  - cases treated
- Limitation: CEA cannot be used to compare interventions with different health outcomes because of its non monetary measurement of outcomes.

Incremental Cost-Effectiveness Ratio

$$ICER = \frac{Incrementd \quad Cost}{Incrementd \quad Effectiveness}$$

Incremental Cost=(Cost of program A) - (Cost of program B)

Incremental Effectiveness
=(Effectiveness of program A) - (Effectiveness of program B)

ICER (e.g., $ per life saved, $ per disability day avoided, or $ per case treated) is used to make decisions. The alternative with the lowest ICER will be chosen.

Problems with CEA

- How about Quality of life ➔ (CUA)

Cost Utility Analysis (CUA)

- Similar to CEA.
- CUA tried to combine the quality and quantity of life in its outcome measures.
- The most commonly used outcome measure in CUA is Quality Adjusted Life Years (QALYs).

CUA (cont.)

- Definition of QALY
  - Number of years at full health that would be valued equivalently to the number of life years as experienced.
- Example:
  - Persons with permanent kidney failure have lower quality of life, therefore, for these people, 10 years of life might be equivalent to 5 QALYs.

CUA (cont.)

- What is the U in CUA?
  - Utility: It refers to level of satisfaction or usefulness that consumers derive from the consumption of goods and services.
- In economic theory, consumers make their purchase decision based on the level of utility per dollar spent.
- Utility is inherently subjective.

CUA (cont.)

- Two limitations of CUA
  - Measurement of utility is very time and resource intensive.
  - Lack of consensus on which measurement methods
    - In general, researchers agree that “choice-based” approaches (e.g., standard gamble, time trade-off) are more appropriate.
- NOTE: QoL is NOT utility

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  - *Problenms with ICER*
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1) The decision criteria under cea

CEA Framework

- Two treatments (trx): new (A) vs. old (B)
- Costs:
  - Pts in the new trx group: $C_{a1}, C_{a2}, \ldots C_{aK}$ → $\overline{C}_A$
  - Pts in the old trx group: $C_{b1}, C_{b2}, \ldots C_{bJ}$ → $\overline{C}_B$
- Effectiveness:
  - Examples of effectiveness measures:
    - Quality-adjusted life years (QALYs)
    - Life year saved
  - Pts in the new tx group: $E_{a1}, E_{a2}, \ldots E_{aK}$ → $\overline{E}_A$
  - Pts in the old tx group: $E_{b1}, E_{b2}, \ldots E_{bJ}$ → $\overline{E}_B$

What Amount of Money Has to Be Invested to Get The expected Benefits ?

The ratio additional Investment / induced health outcomes :

Two independent populations matched by the propensity score method

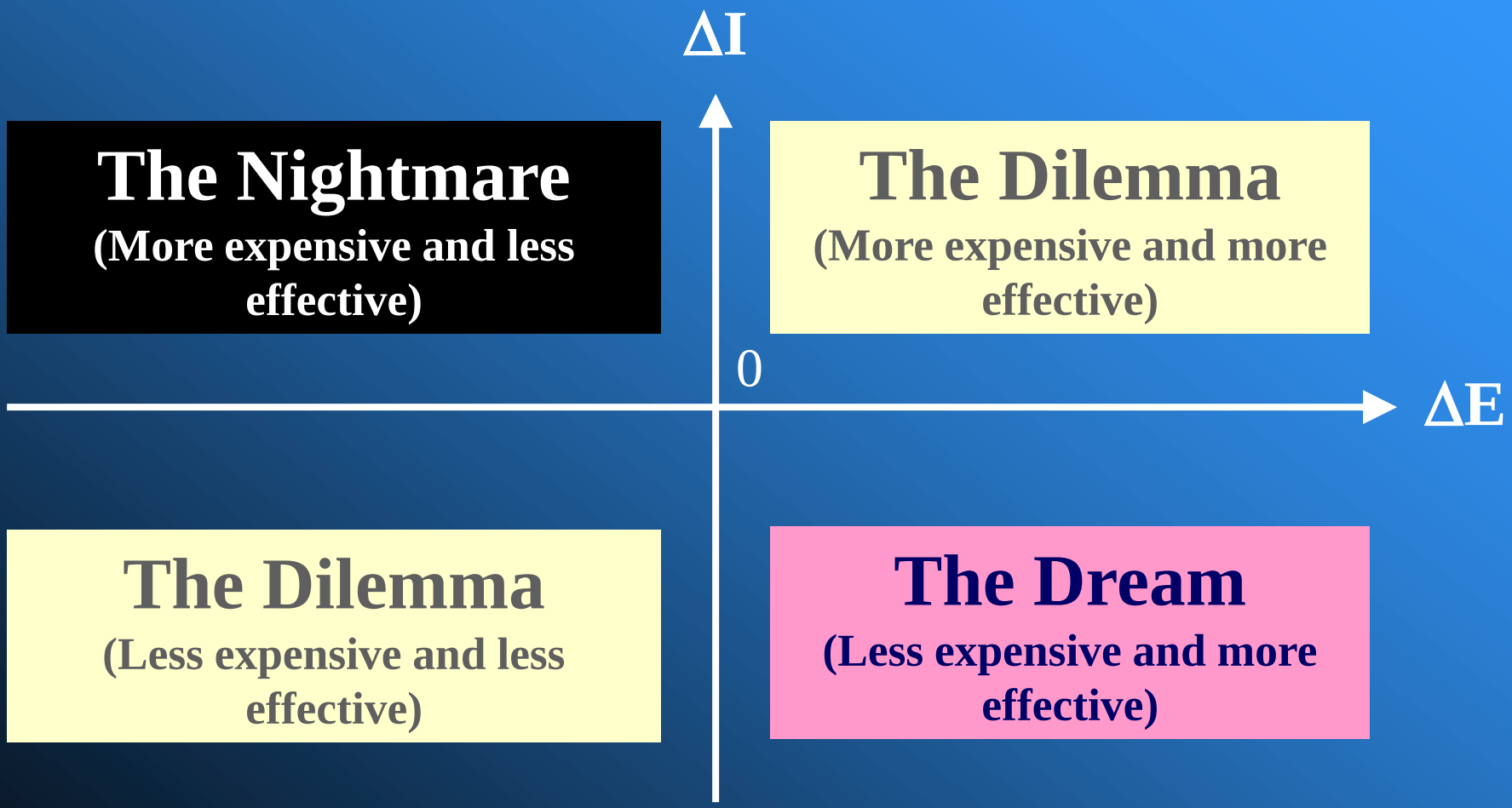
Before group (N=420)
mean : $\overline{E}_{Avant}, \overline{C}_{Avant}$

After group (N=420)
Mean: $\overline{E}_{Après}, \overline{C}_{Après}$

Incremental cost effectiveness ratio

$$R = \frac{\Delta C}{\Delta E} = \frac{\overline{C}_{Après} - \overline{C}_{Avant}}{\overline{E}_{Après} - \overline{E}_{Avant}}$$

Ranking Treatments According to Their Incremental Cost-Effectiveness Ratio



How to Decide If : « The Costs are Worth the Effort »?

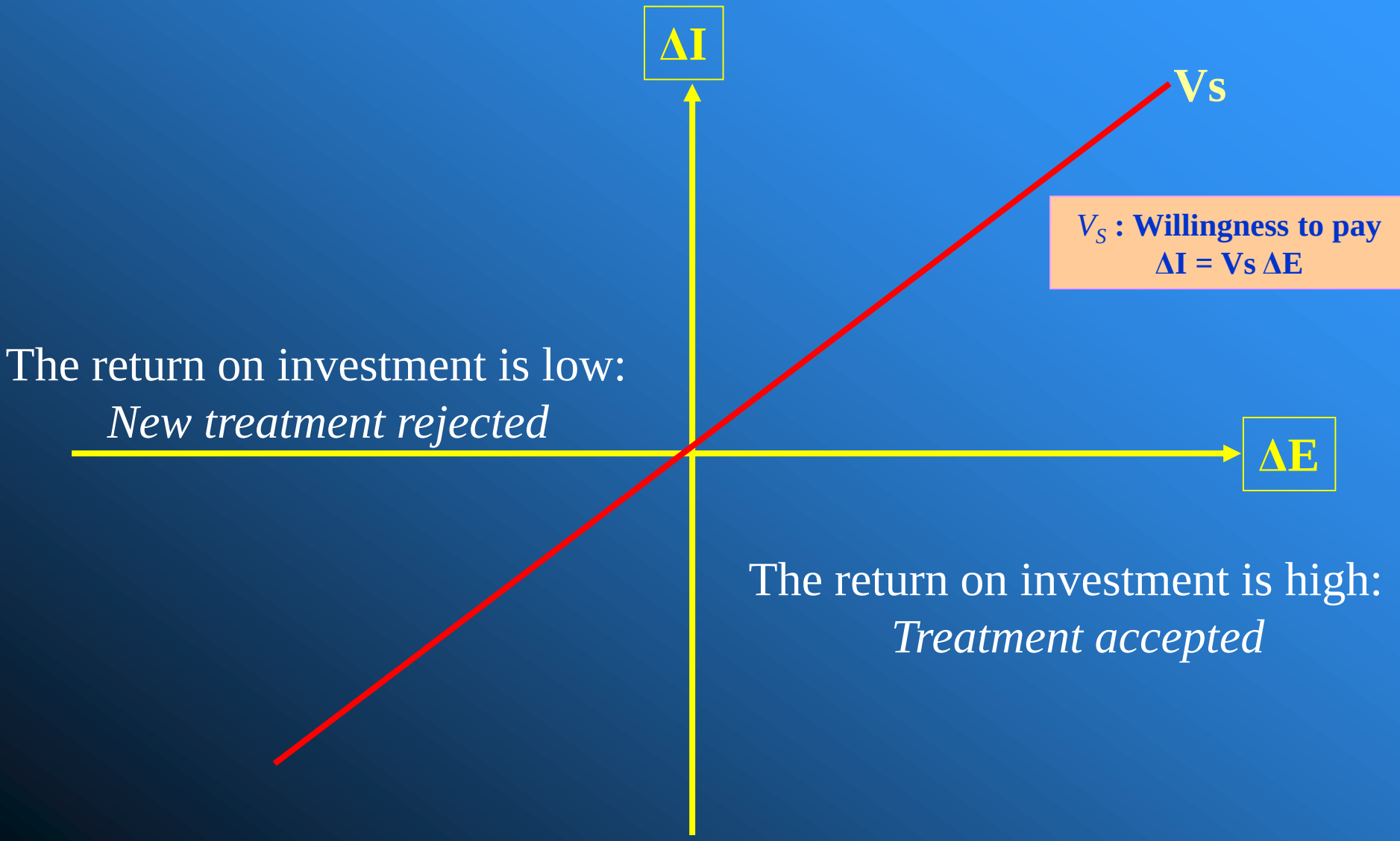
Two possible reference criteria:

- **MARGINAL WILLINGNESS TO PAY: the meximum amount which the community is willing to pay to gain one unit of effectiveness**
- **PRECEDENTS: the cost-effectiveness ratios of new or established drugs which have been accepted for reimbursement or re-evaluated in the recent past**

Making Decisions Using ICER

- If the ICER doesn't fall into the quadrant of dominating or dominating strategy, then decision makings based on CE-ratio become a bit tricky.
- Rule 1: value judgement specified by an organization
  - $20,000 per QALY used in Ontario guidelines
- Problems?

Limits of Solidarity

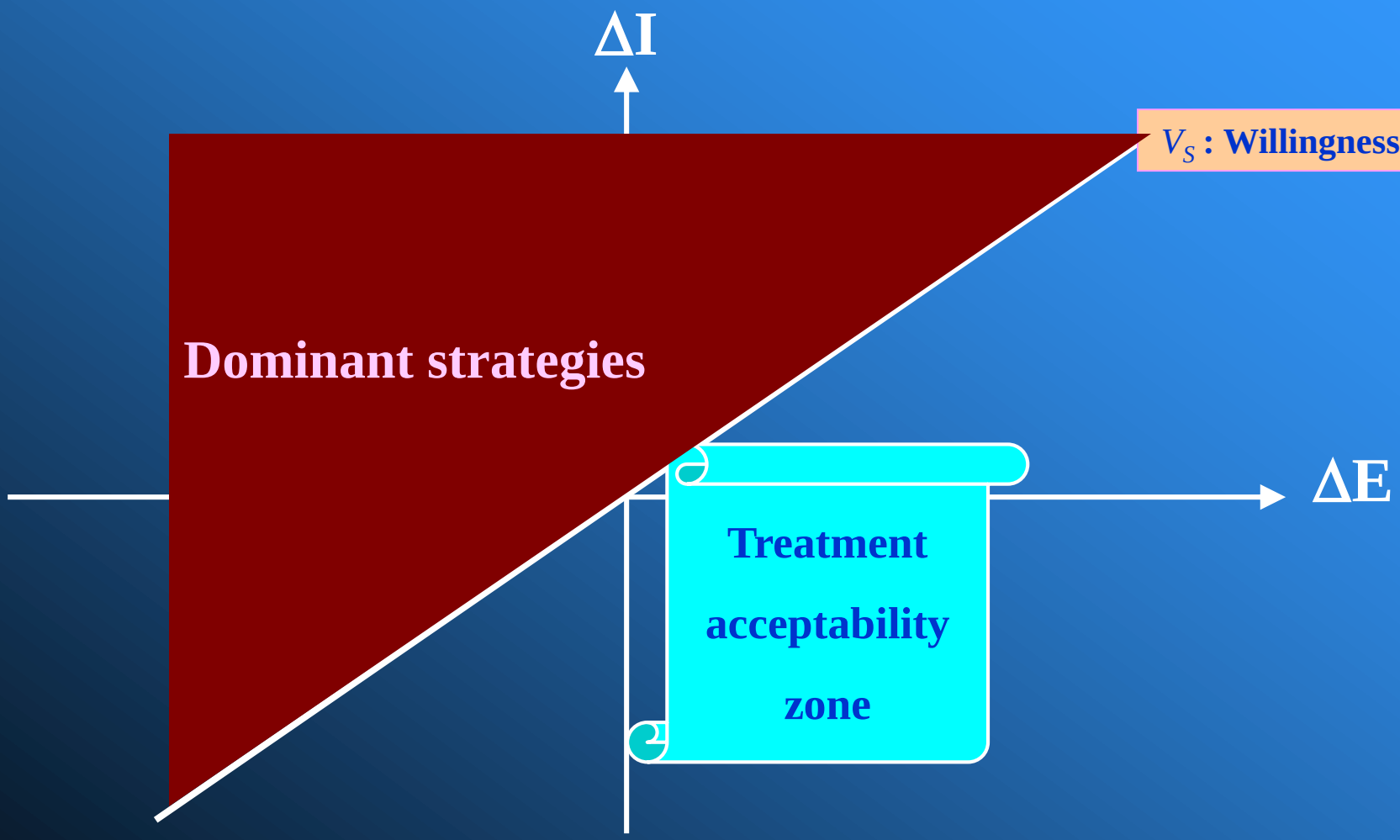


V_S : **Willingness to pay**
ΔI = Vs ΔE

The return on investment is low:
New treatment rejected

The return on investment is high:
Treatment accepted

How Much are the Fit Willing to Pay?



Making Decisions Using ICER (cont.)

- Rule 2: comparison with the commonly used medical procedures.
- Rationale: Society should be willing to pay as much for new procedures/technologies as it does for procedures that are currently in common use.

→League tables

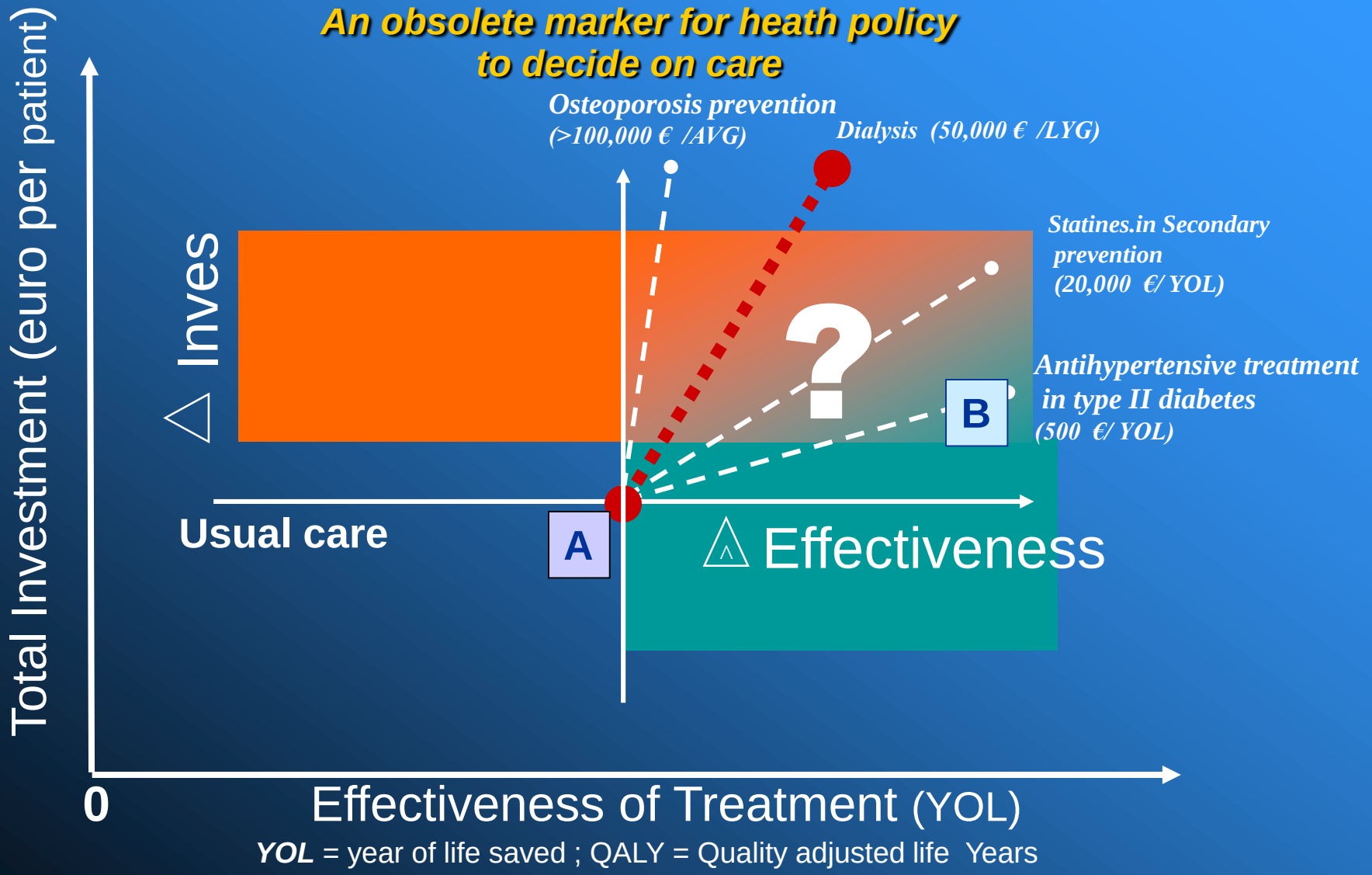
- Problems?

League Table Example

Treatment	$ QALY
Coronary artery bypass surgery for left main coronary artery	$ 4,200
Treatment of severe hypertension in males age 40	$ 9,400
Treatment of mild hypertension in males age 40	$ 19,100
Estrogen therapy for postmenopausal symptoms	$ 27,000
Hospital dialysis	$ 54,000

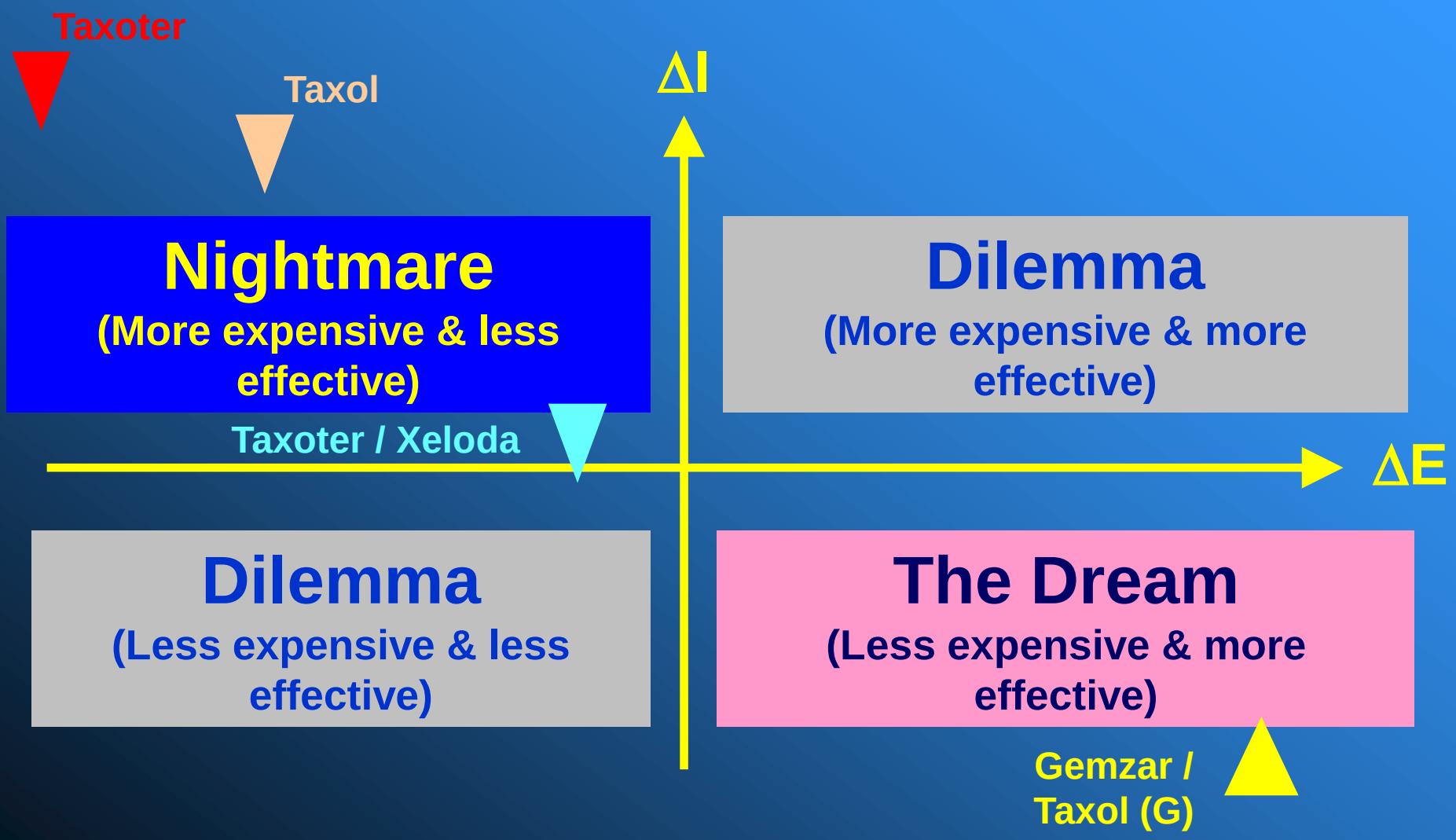
Threshold :
50,000 € per Year of Life Saved

An obsolete marker for heath policy to decide on care



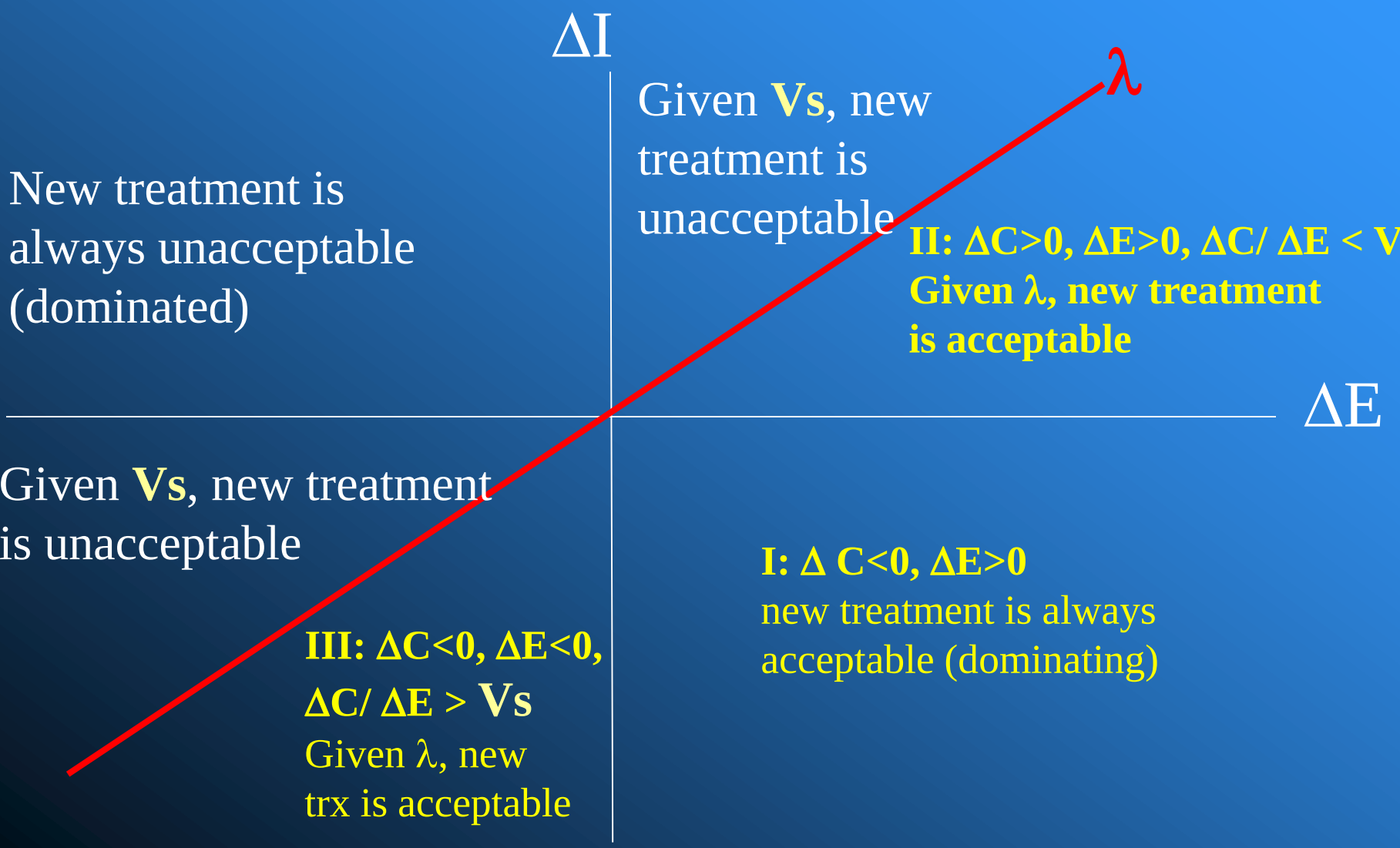
YOL = year of life saved ; QALY = Quality adjusted life Years

An Example in Metastatic Breast Cancer

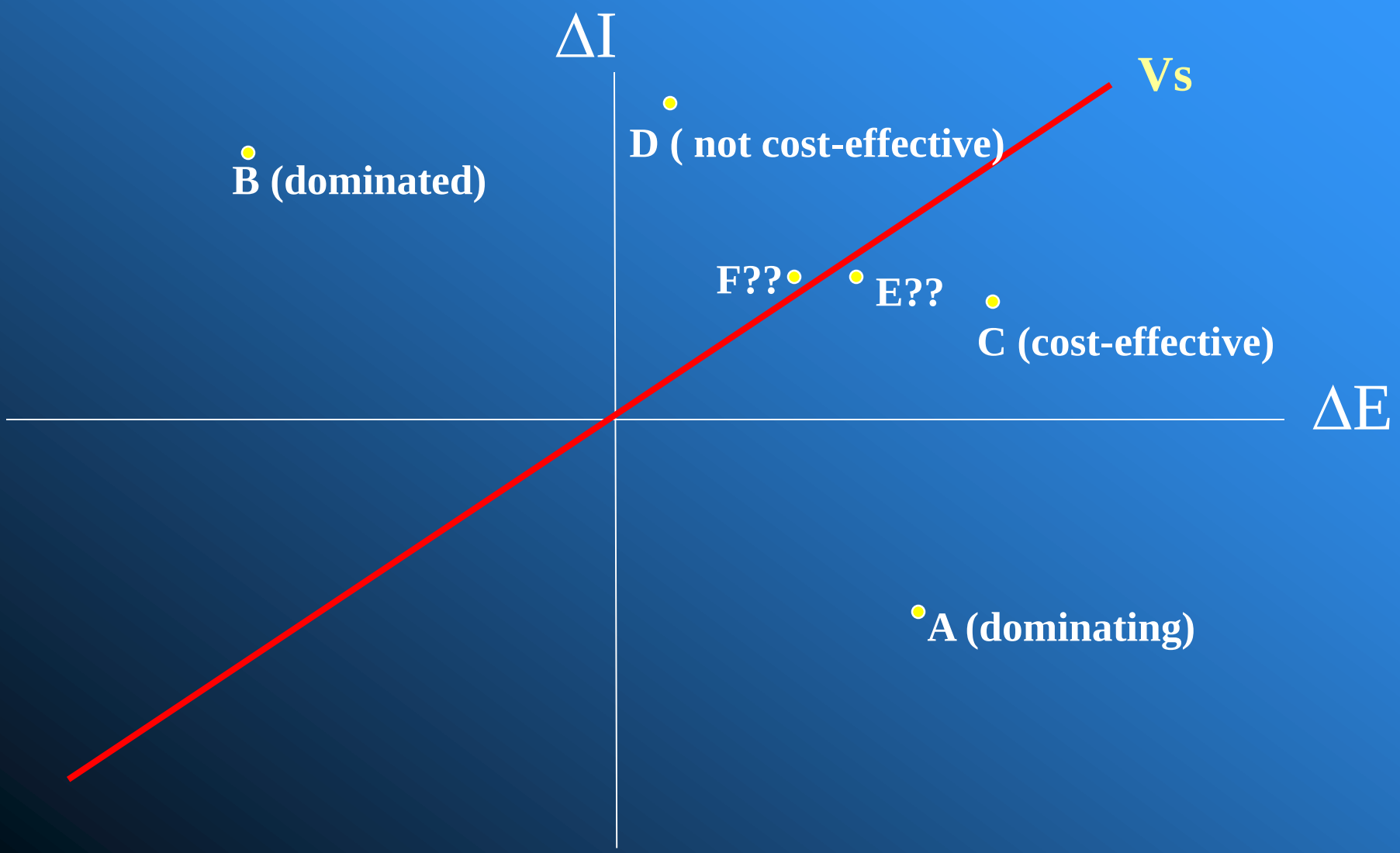


2) Statistical problems raised by cost effectiveness analysis

CE-Plane


ΔI
ΔE
λ
New treatment is always unacceptable (dominated)
Given Vs, new treatment is unacceptable
II: ΔC>0, ΔE>0, ΔC/ ΔE < V
Given λ, new treatment is acceptable
Given Vs, new treatment is unacceptable
III: ΔC<0, ΔE<0, ΔC/ ΔE > Vs
Given λ, new trx is acceptable
I: Δ C<0, ΔE>0
new treatment is always acceptable (dominating)

CE-Plane


ΔI
Vs
D (not cost-effective)
B (dominated)
F??
E??
C (cost-effective)
ΔE
A (dominating)

Recent Advances in CEA - 1

- Estimate confidence interval of ICER
- Statistical Methods:
  - Box method
  - Delta Method (Taylor Series Method)
  - Fieller Theorem Method
  - Nonparametric Bootstrap Method
  - ….

Incremental Cost-Effectiveness Ratio (ICER)

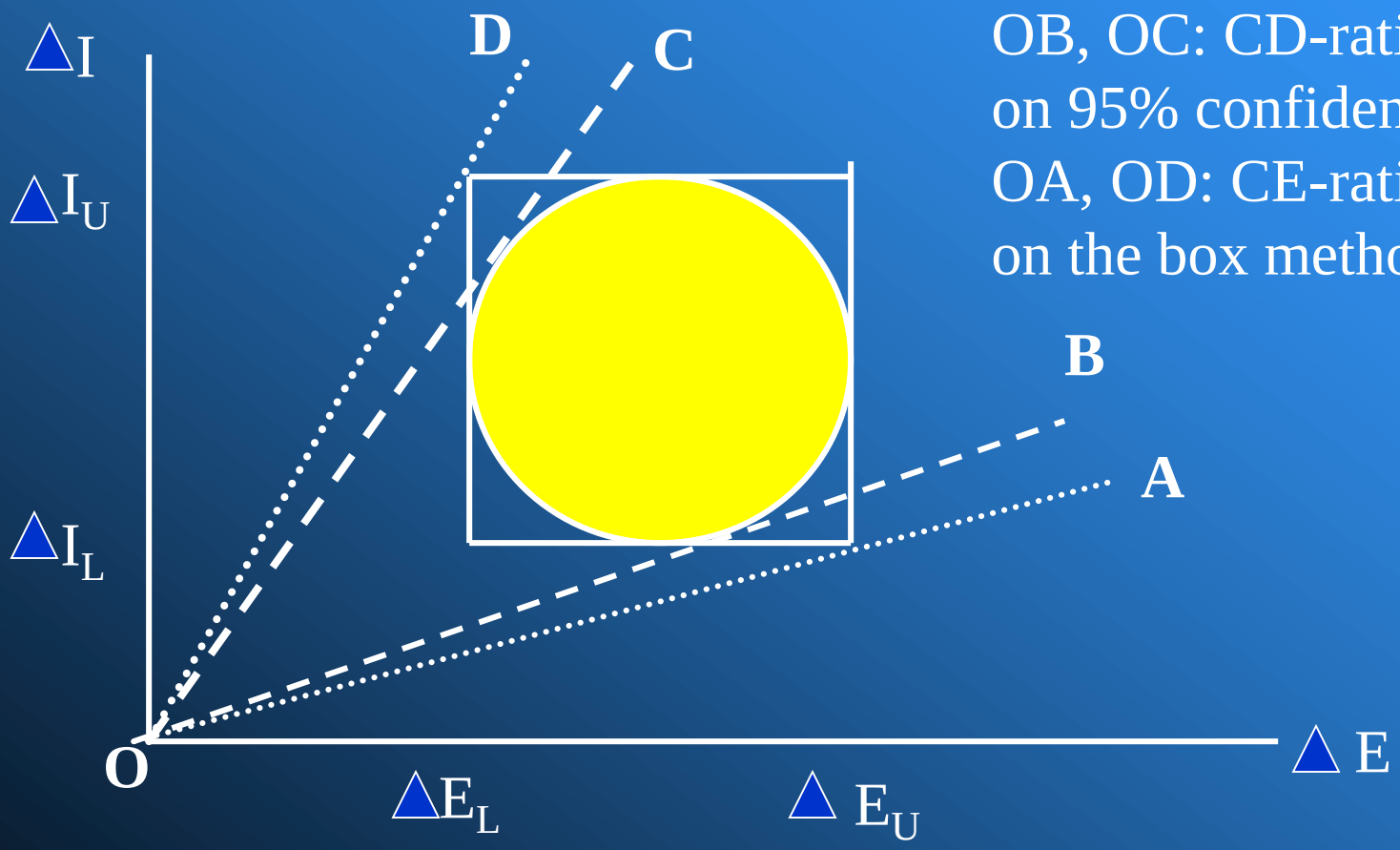
$$ICER = \frac{\mu_{CA} - \mu_{CB}}{\mu_{EA} - \mu_{EB}} = \frac{\mu_{\Delta C}}{\mu_{\Delta E}}$$

Making inference about the true (but unobservable) population ICER

$$\hat{ICER} = \frac{\overline{C_a} - \overline{C_b}}{\overline{E_a} - \overline{E_b}} = \frac{\Delta C}{\Delta E}$$

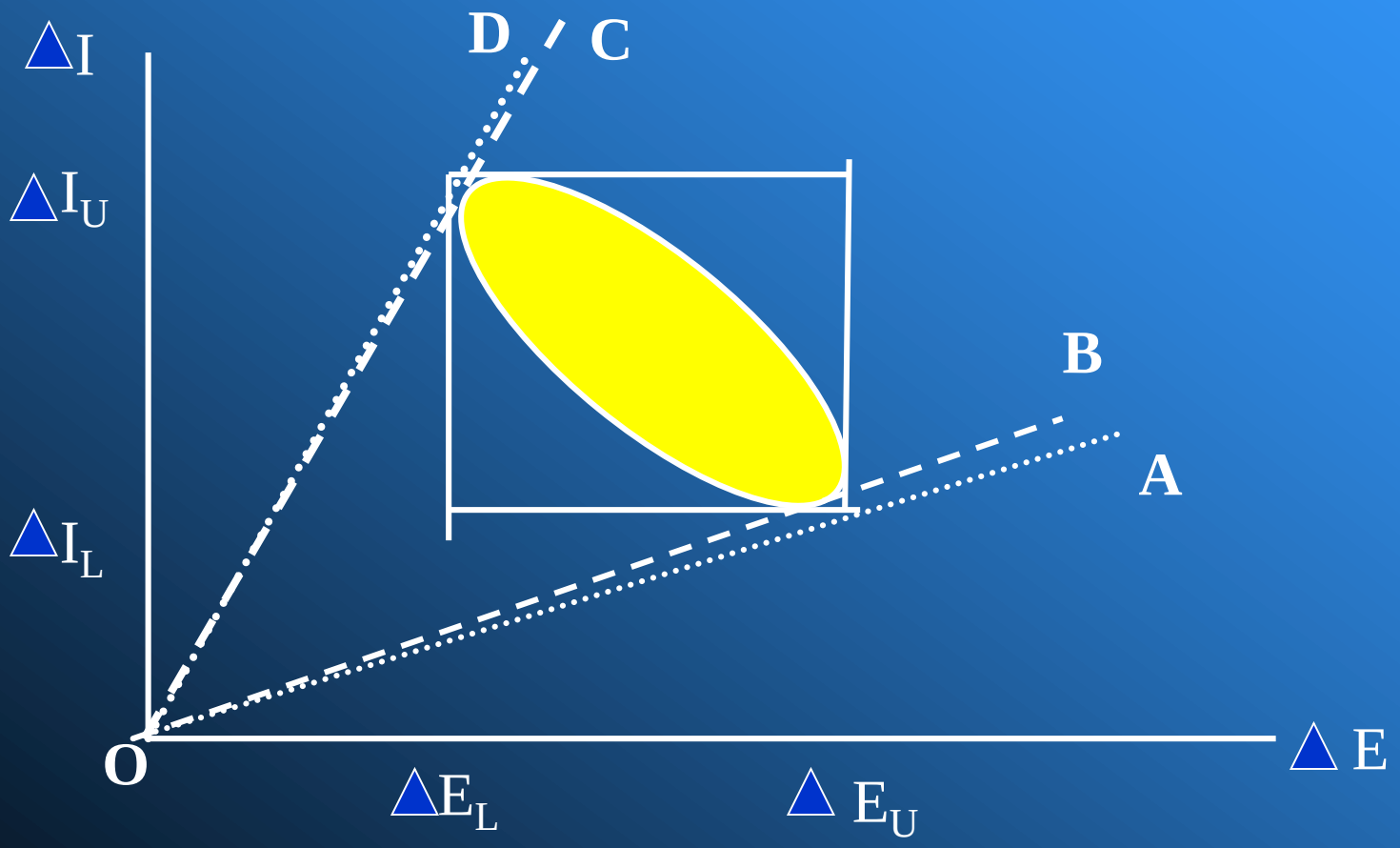
- Decision Rule: If $\hat{ICER} < \lambda$, then the new treatment is cost-effective

95% Confidence Ellipsoid

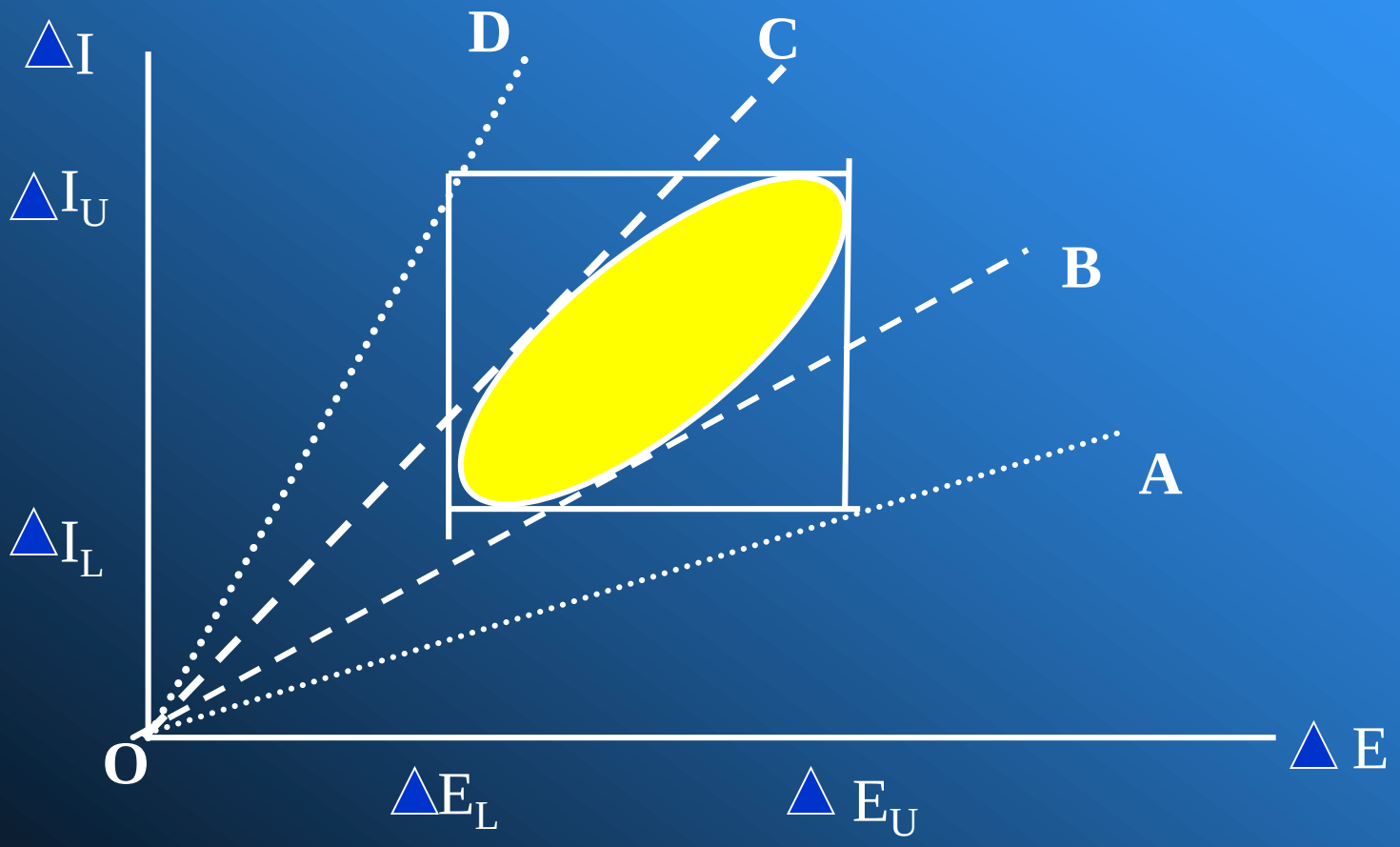


OB, OC: CD-ratio based on 95% confidence ellipsoid
OA, OD: CE-ratio based on the box method

Negative Correlation



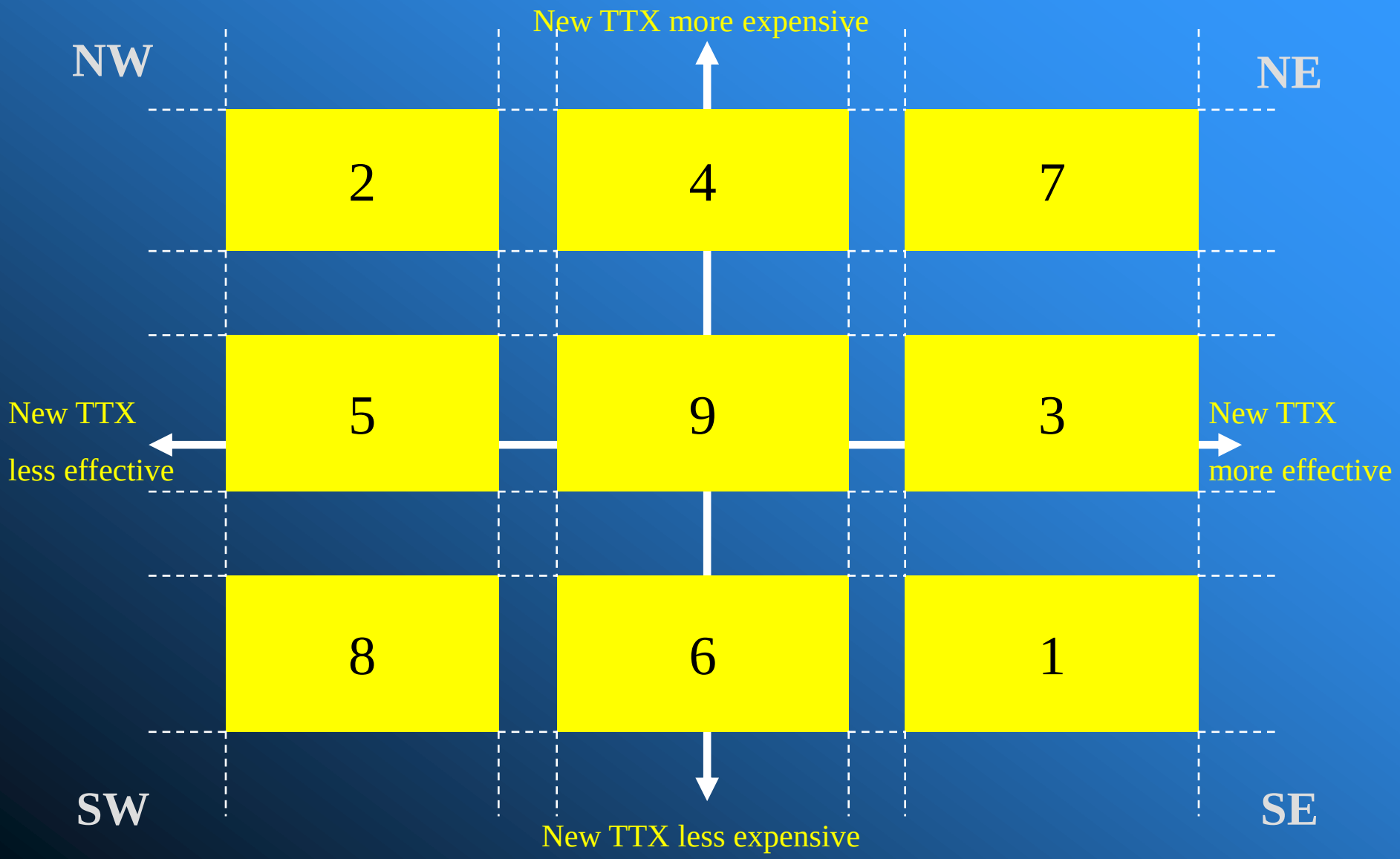
Positive Correlation



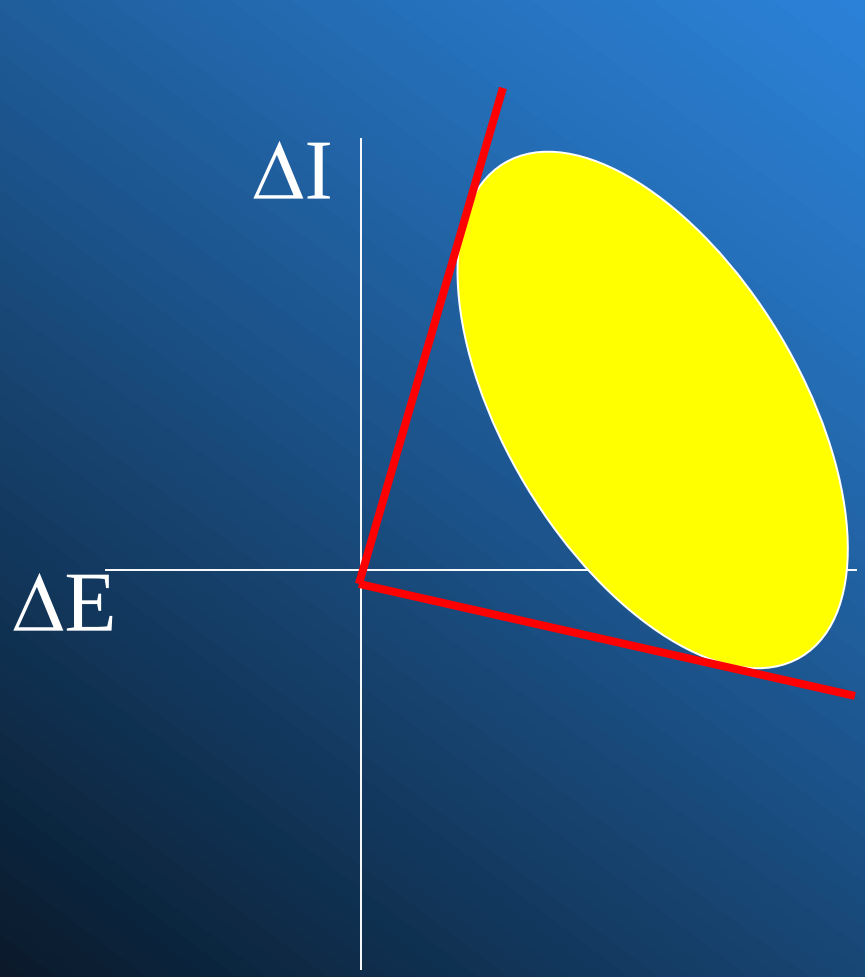
Inherent Difficulties of Reasoning in Terms of Ratios

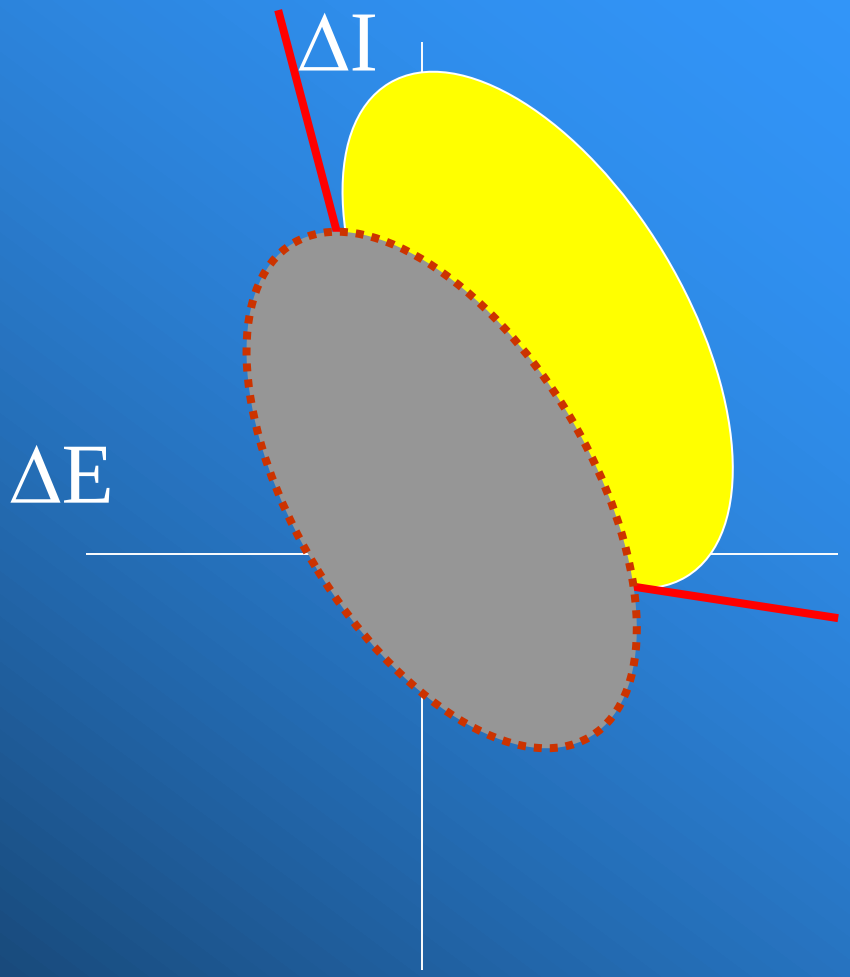
- Negative ratios are difficult to interpret
- The confidence intervals are only meaningful if ΔE is positive
- → Solution: the net health benefit approach

Cost-Effectiveness Ratios Matrix

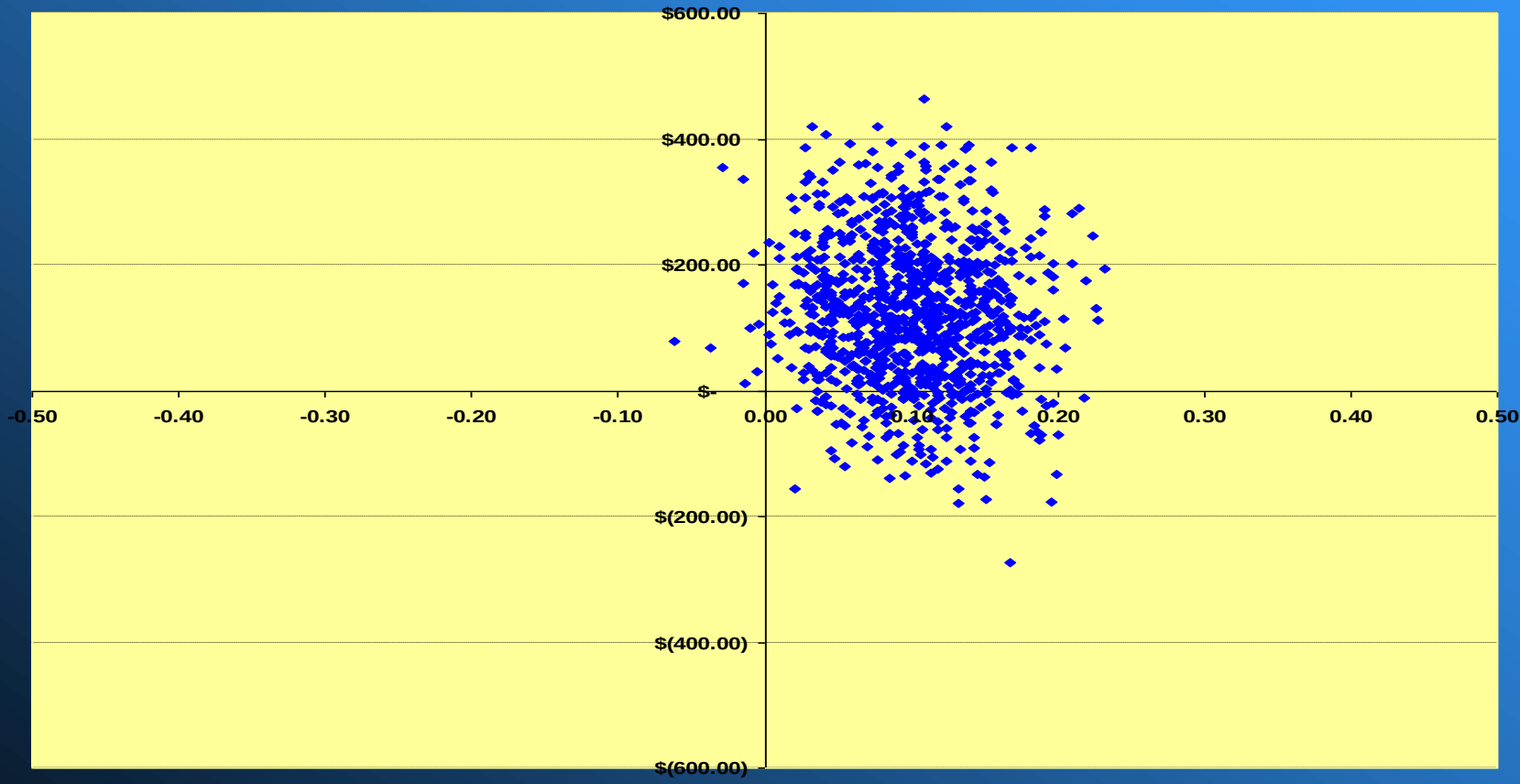


Problems?



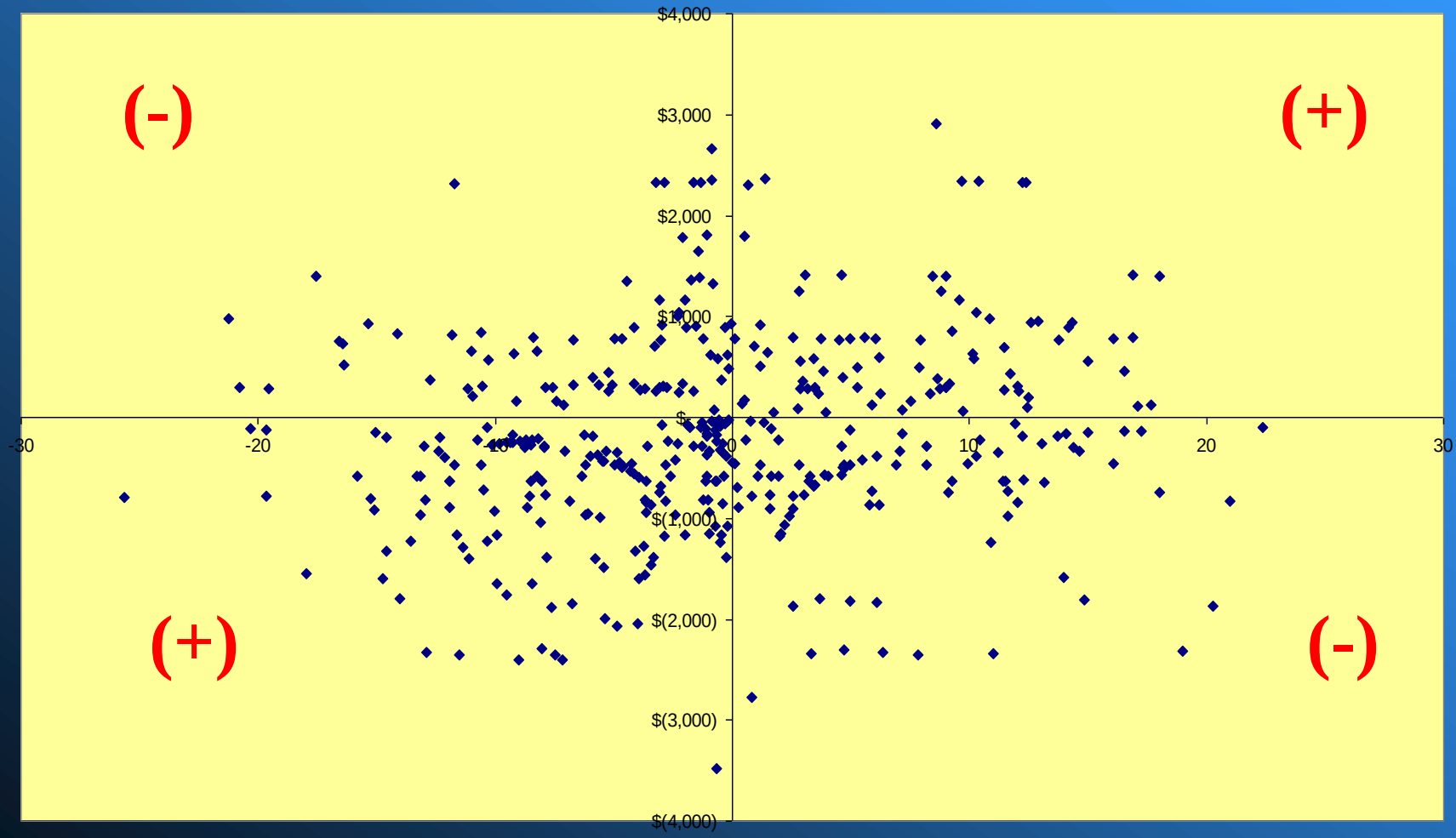


Non-parametric Bootstrap



Percentile method → CI = [2.5th – 97.5th]

Problems?



The Net Benefit Approach

A Need: To take hold of the uncertainty which presides over the rules of the game

- The value (Vs) allocated by the Society to an amount of additional effect is **socio-political value** which the evaluator cannot judge.
- The results must be analysed in light of the results of the different **possible willingness to pay** from the purchaser by constructing an acceptability curve for the treatment by the statutory auithorities.
- This curve shows the probability that this treatment will considered to be **efficient** by the authorities for all possible values of Vs.
- **Estimation procedure**: generation of ΔE, ΔI couples bootstrap B – by the proportion of points beneath the line for all values of V.

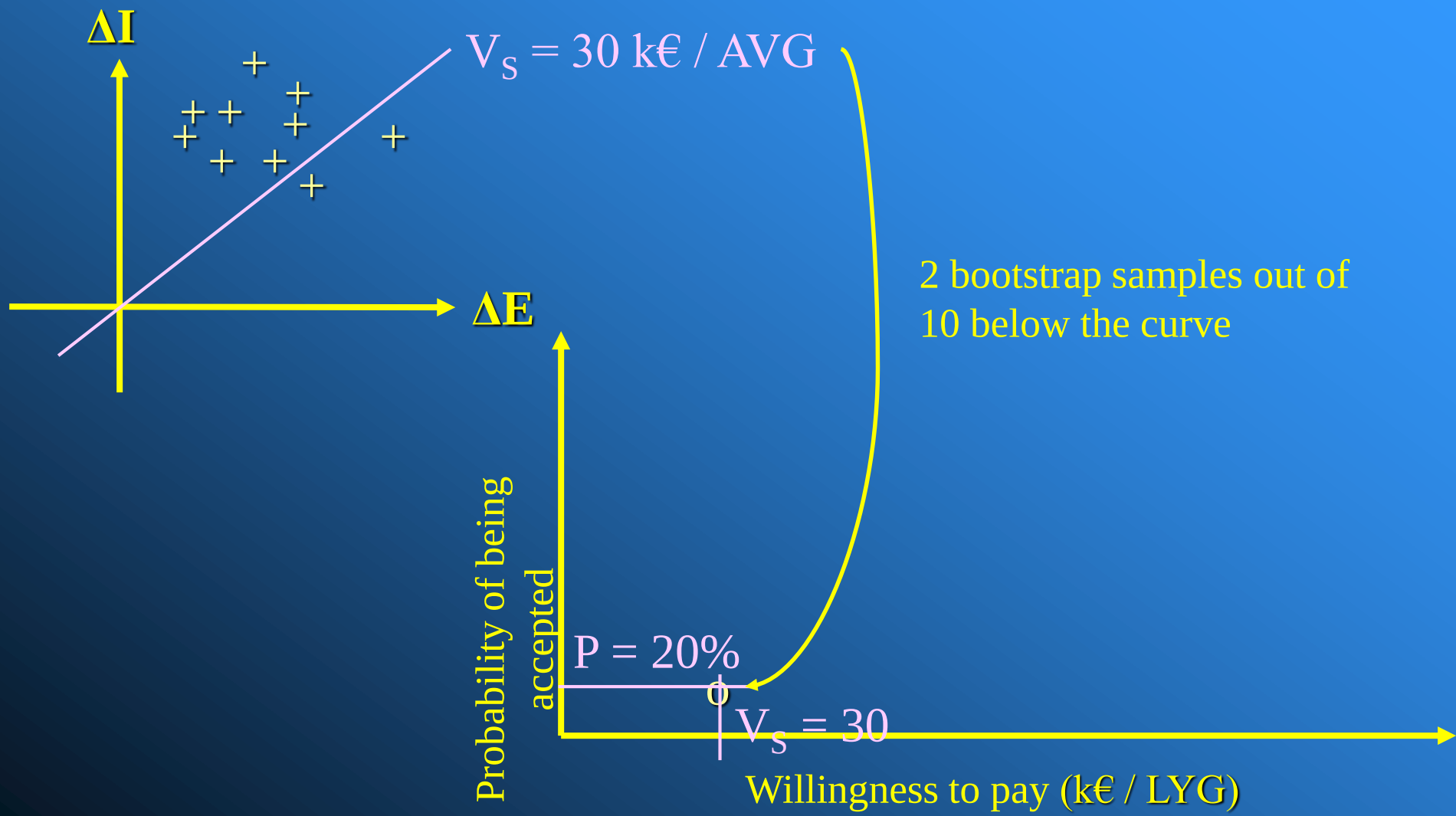
Bootstrap World

Four stage process:

1. Bootstrap n_c cost/effect pairs from the control group: calculate means
2. Bootstrapp n_T cost/effect pairs from the treatment group: calculate means
3. Calculate the bootstrapped ICER from these bootstrapped means
4. Repeat many times to create the bootstrap estimate of the ICER sampling distribution

Acceptability for Reimbursement by the Legal Authorities,

depending on the financial effort are willing to employ



Acceptability for Reimbursement by the Legal Authorities,

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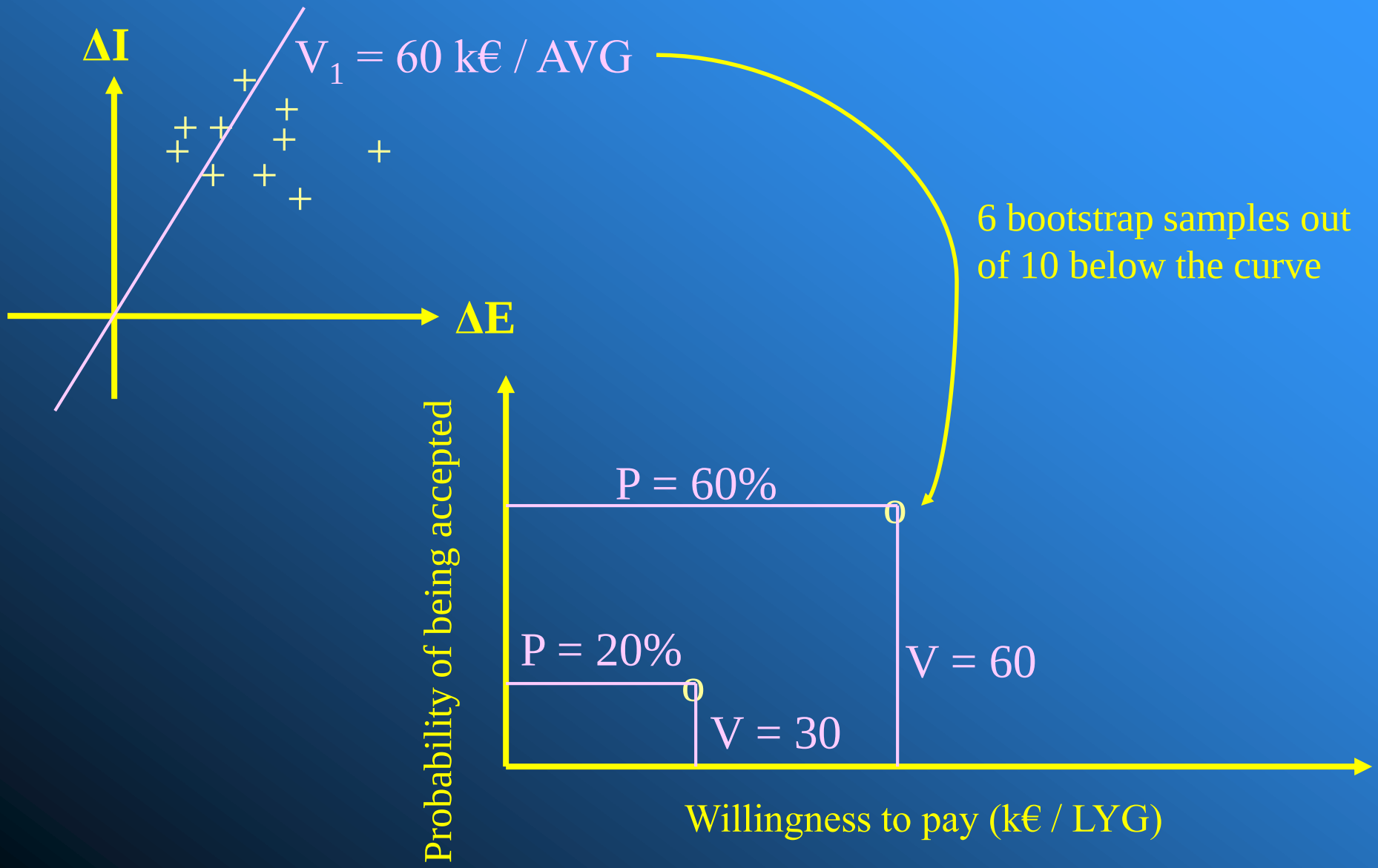
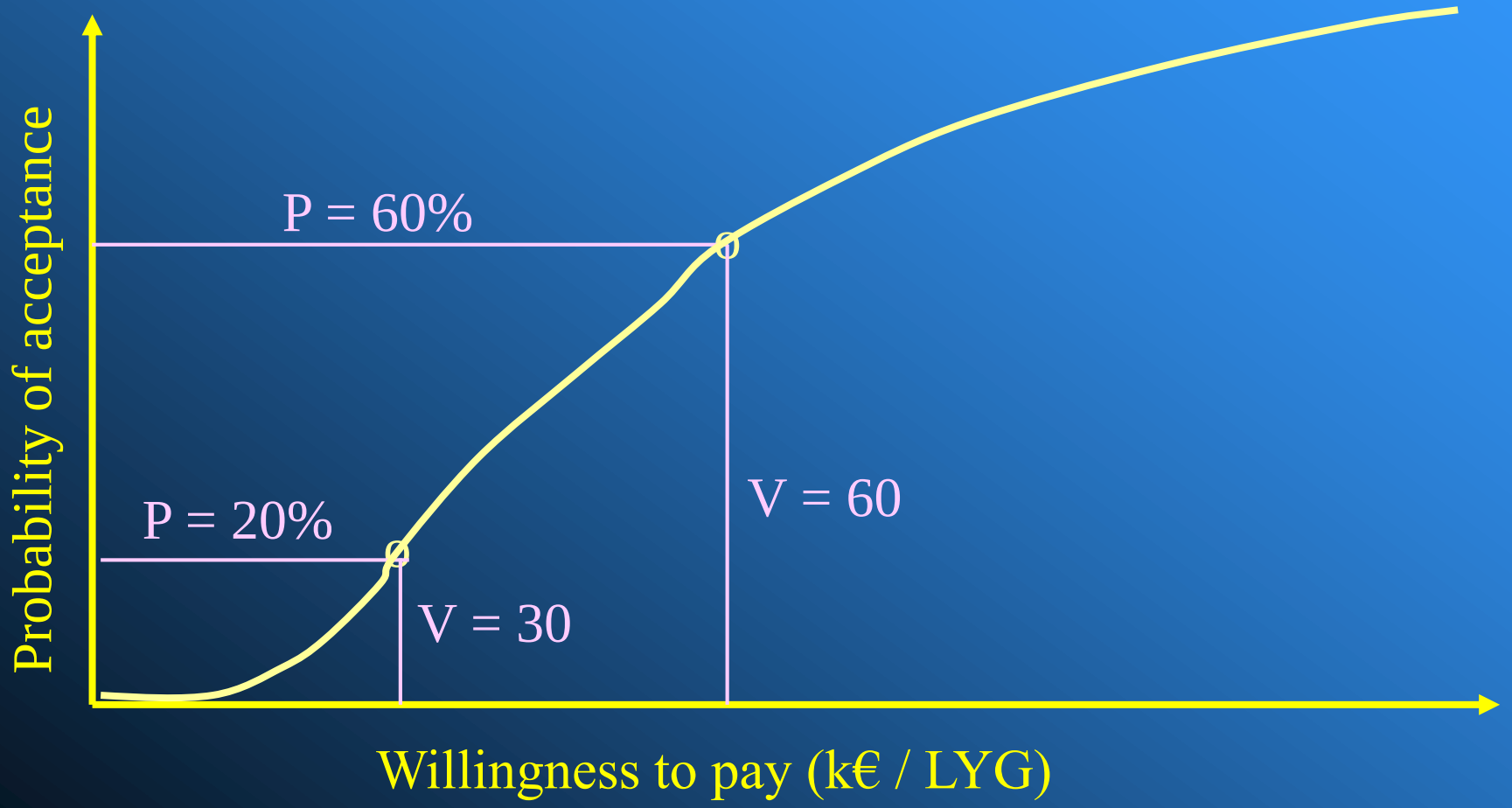
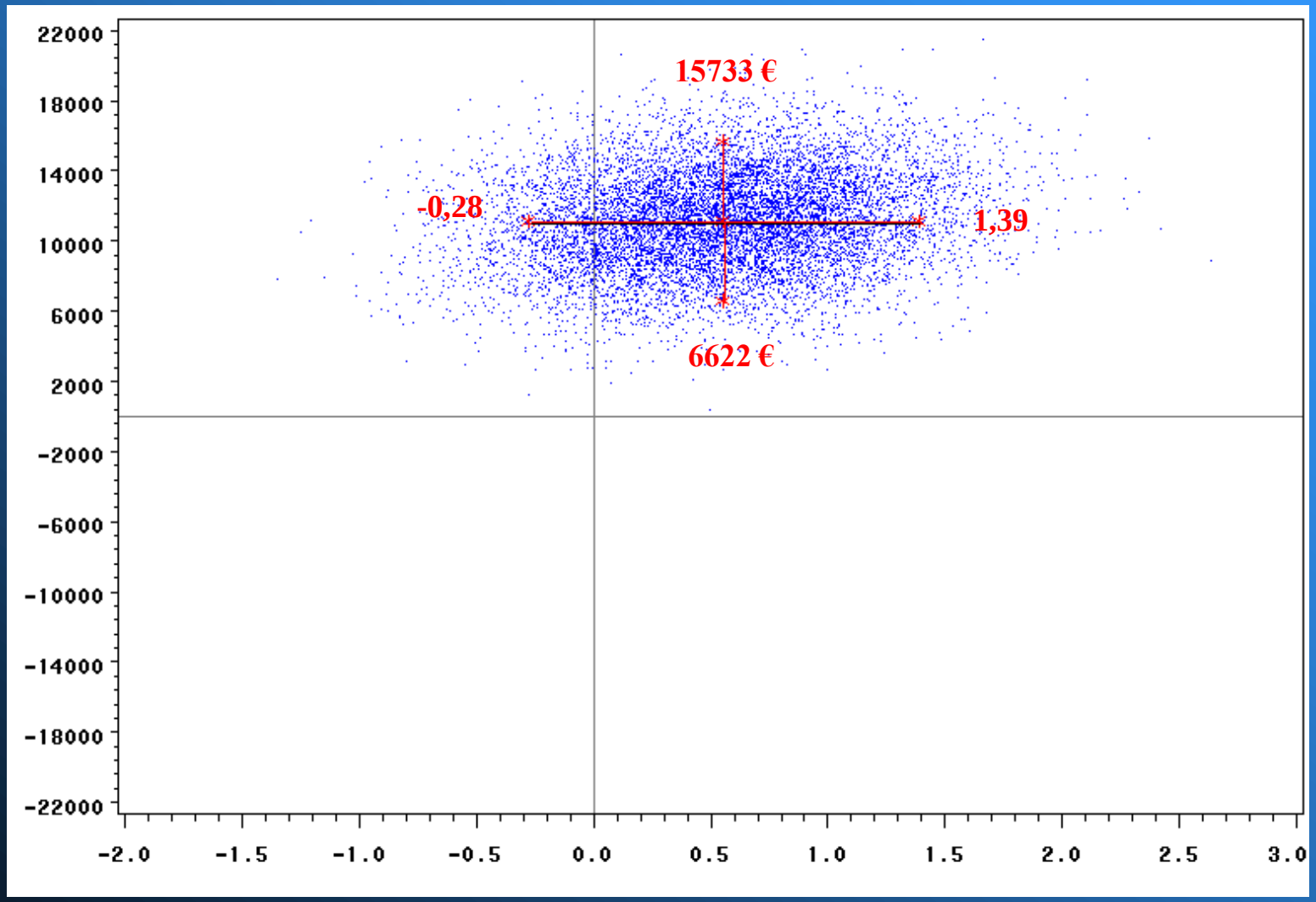


Reimbursement Acceptability Curve for the Statutory Authorities: « *CARAT* »

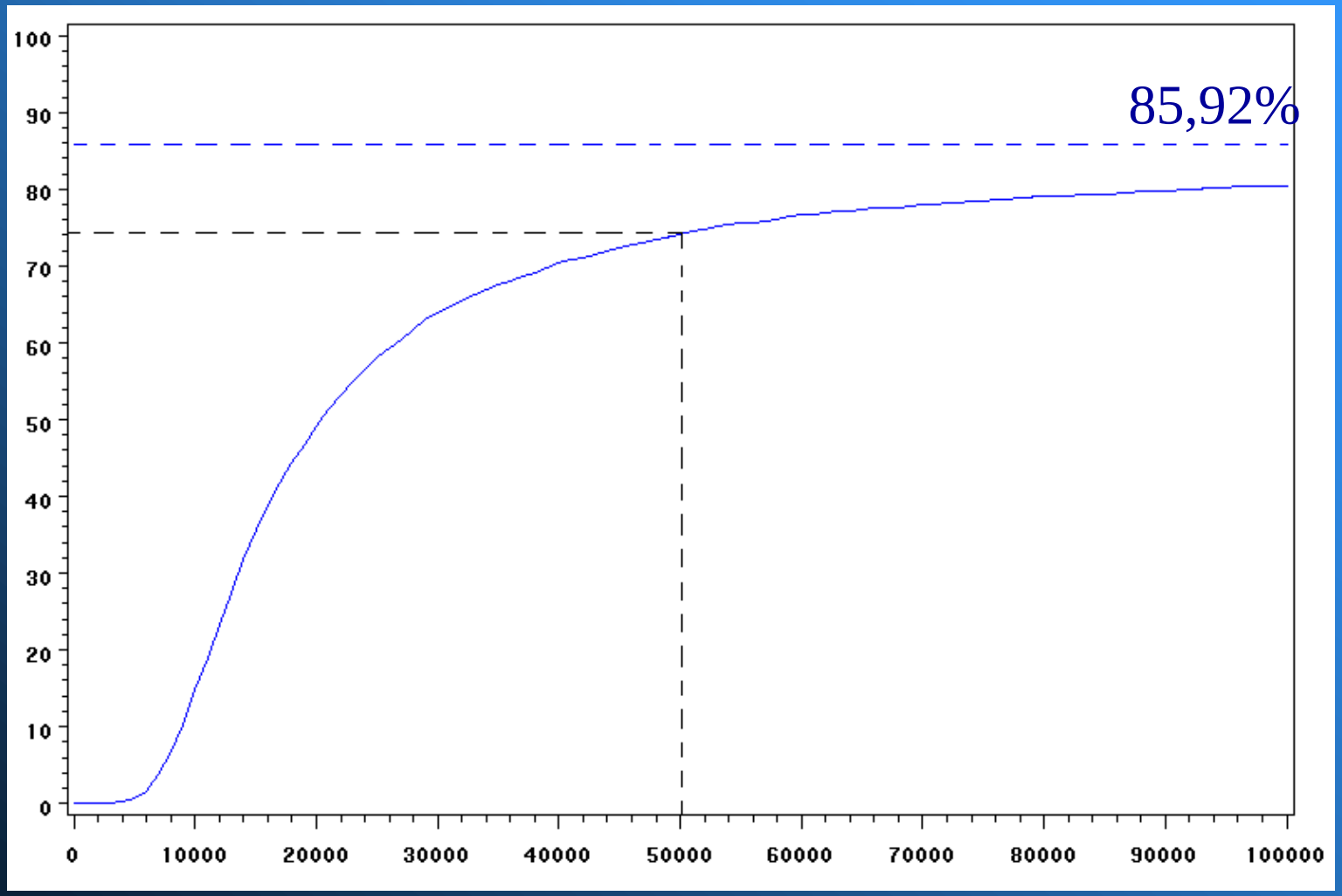
A coherent tool for the public bodes



Dispersion of Incremental Cost Effectiveness Ratios after Resampling



Probability of Making the Correct Choice in Terms of Community Efficiency when the new TTX is Used in Preference to Conventional Treatments



Plan of the Intervention

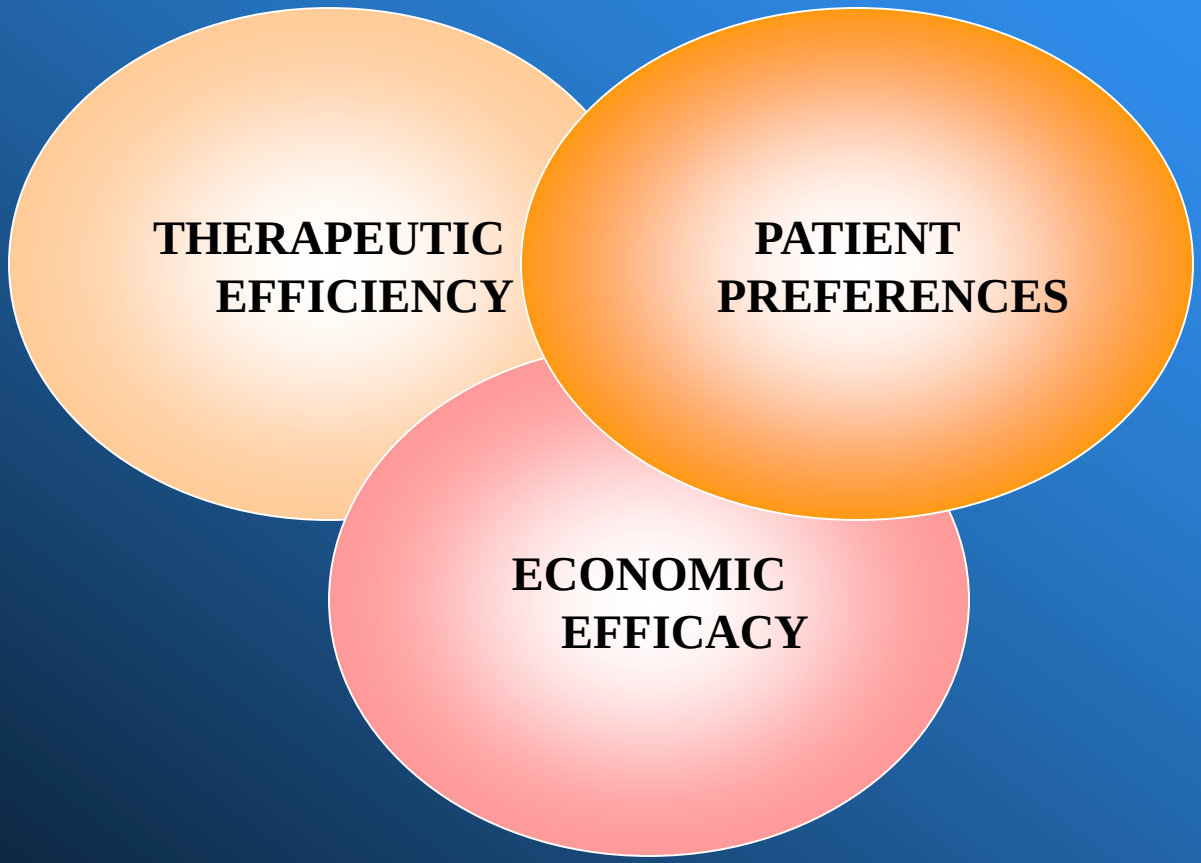
- ***EVIDENCE***
  - *Evidence based medicine…*
  - *Types of evidence and bias ?*
  - *How to move from experimental models to real life?*
- ***METRICS***
  - ***Measures of heath outcome***
  - *Why consider the cost?*
  - *What are the types of economic analysis?*
- ***ASSESSMENT CRITERIA***
  - *Decision criteria under CEA*
  - *Problenms with ICER*
  - *Net public health benefit*
- **HOW TO INFORM THE POLITICAL DECISION MAKING?**

HOW TO INFORM THE POLITICAL DECISION MAKING?

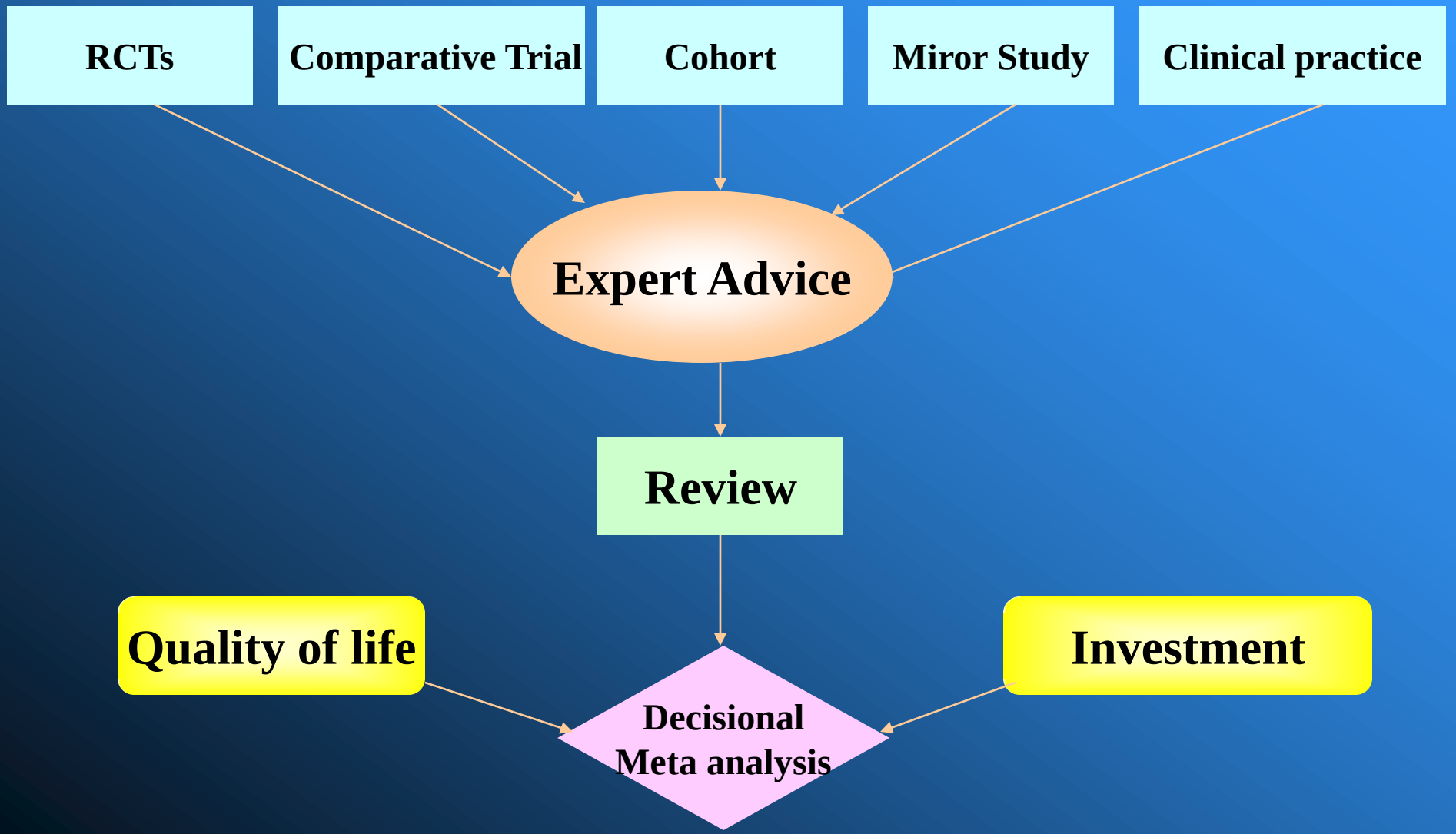
Analytical Approaches of Economic Evaluations

- Decision model-based approach
  - Information pooled from multiple sources (e.g., literature, expert opinion, …)
- Trial-based approach
  - Patient-level data
- Combined

An Imperative : Collect All Information Which Contribute to the Decision Making



Generalised Review of Probing Data



Meta Decision Analysis: A Tool to be Used in First Line

- To structure the information in a single analytical framework
- To simultaneously integrate benefits, risks and costs
- To quantitatively estimate the frequency of evolutionary events and adverse effects
- To identify the pathways of the patient's management and to link the costs

http://www.mrc-bsu.cam.ac.uk/bugs/

… To Collect the Evidence and Estimate the Expected Efficacy and the Actual Effectiveness

- To synthesise heterogeneous clinical endpoints with a composite morbid-mortality index
- To reintroduce patients preferences or citizen wills in the decisional process at an individual or collective level
- To extrapolate the results to different populations or settings
- To isolate the key variables and to specify the uncertainty surrounding them
- To present the results to decision makers as probabilities for the intervention to be cost effective given a maximum willingness to pay per unit of effect

Conclusion

The implementation of databases fed by professionals based on individual data, deeply upsets the assessment methods.

- New endpoints are introduced
  - QoL assessment
  - Estimates of the additional investments required to obtain the expected or actual clinical benefits

- A new ethic of our duties arises:

« prodigate the best » per euro invested