HEALTH ECONOMICS WORKSHOP
Le Caire 21 Mai 2010

Introductory Pharmacoeconomic Principles

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Plan of the Intervention

- *INTRODUCTION : ASCLEPIOS vs HYGIE*
- *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*
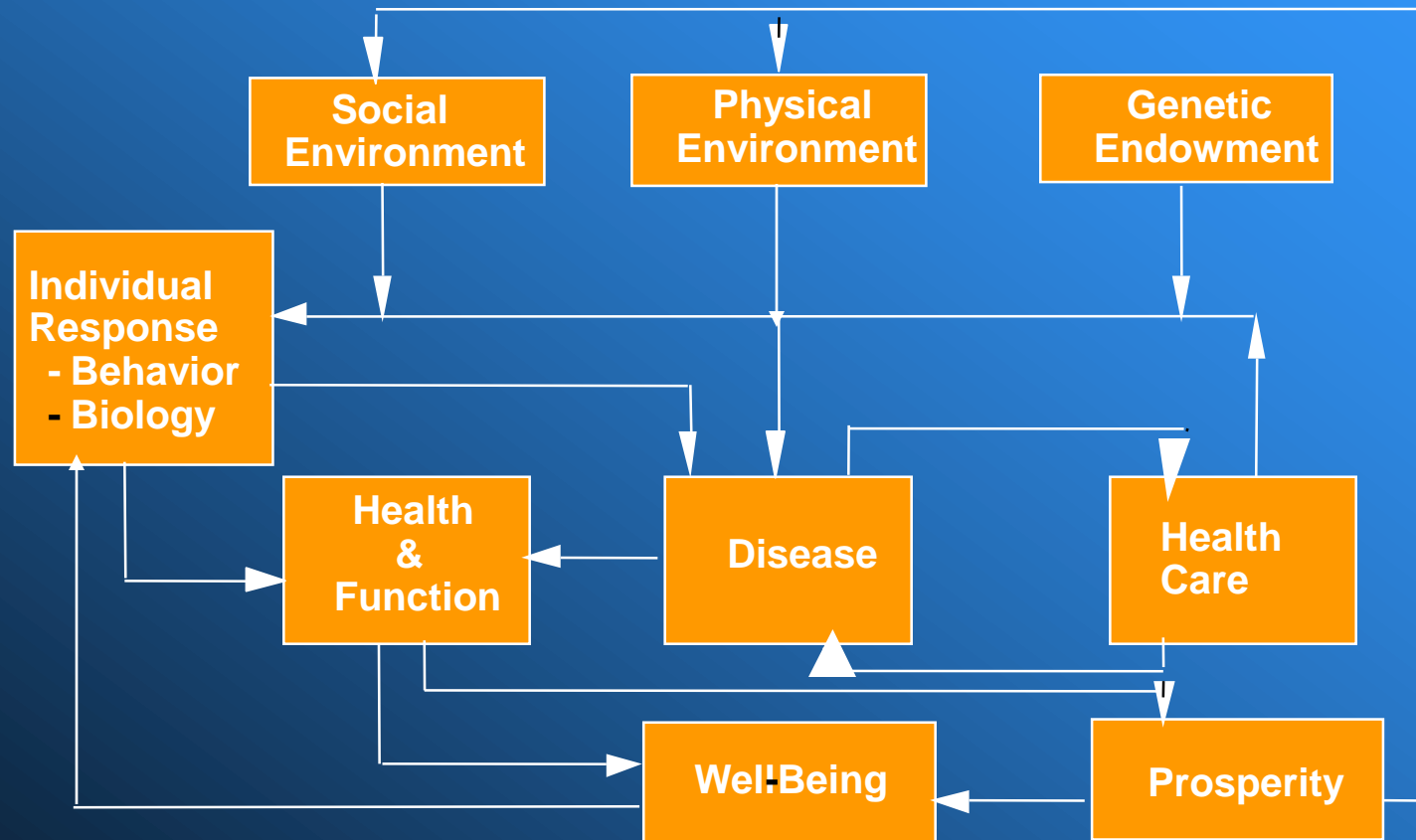- *TRANSLATING ANALYSIS INTO POLICY*

Balance Between External Intervention and the Well-Lived Life

- What are the conditions which lead to the pain and penalty of disease?
- What are the means for the removal of those conditions when they are discovered?
- What are the methods of making known to the uninformed, the facts:
    - That many of the conditions are under our control,
    - That poverty is the shadow of disease,
    - And wealth the shadow of health."

Determinant of Heath : Definitions

- An element that identifies or determines the nature of something or that fixes or conditions an outcome" (Webster, 1981).

- Determinants are Summaries of Constructs that are Associated with Health Impact

Evans & Stoddart Model of Health and Well Being

Source: RG Evans & GL Stoddart, "Producing Health, Consuming Resources"

Social Environment

Construct	Health Impact
Family Structure	Children's physical and mental health
Educational System	Years of formal education strongly related to age-adjusted mortality
Social Networks	Strong inverse correlation between number and frequency of close contacts and all cause mortality
Social Class	Clear relationship between social class and mortality after adjusting for smoking and income
Work Setting	Involuntary unemployment negatively affects mental and physical health
Level of Prosperity	Economic prosperity is correlated with better health

* Improving Health in the Community, IOM, 1997

Physical Environment

Construct	Health Impact
Urban/Rural	Cancer rates Comorbidities
Poor Housing and Overcrowding	Violence Infectious disease Mental health problems
Safety at home/work	Injury rates
Design of vehicles and roadways	Crash and survival rates
Exposures to toxins	Lung disease Cancers

* Improving Health in the Community, IOM, 1997

Genetics

- Genomics: Study of functions & interactions of all genetic material (DNA) belonging to an organism

- Potential impact of genomics on health
  - Target/alter interventions based on genetic susceptibility
  - Determining the risk for developing a disease or condition
  - Developing better medical treatments

Prosperity

Construct	Health Impact
Socioeconomic Status (Income and Education, Class)	Better health associated with increasing income, education, social class
Unemployment	Unemployment associated with financial instability leading to poorer health.
Access to good nutrition/food	Shortage or lack of food leads to malnutrition.
Community Economy	Healthy economy provides jobs, products, services.

Comparing Clinical Research and Health Outcomes Research

Clinical Research

- **Objective**
  - Evaluates *safety* and *efficacy* of an intervention
- **Methods**
  - RCTs with well-defined control group. Can use surrogate markers as a proxy for efficacy. Limited generalizability, as entry criteria are tightly controlled, patient population is homogeneous, and strict protocols are used
- **Study time frame**
  - Short (several months)

Health Outcomes Research

- **Objective**
  - Evaluates *effectiveness* and *efficiency* of an intervention
- **Methods**
  - Retrospective analyses or prospective studies, including clinical trials, observational, or naturalistic studies. Broader generalizability, since patient population is heterogeneous; no strict protocol; reflects typical clinical practice
- **Study time frame**
  - Long (can include years of f/u)

Primary Objective

- *To provide health care stakeholders with useful tools to assist in decision making*

- *Clinical, humanistic or patient-reported, and economic outcomes are all needed to determine the value of competing therapies in order to make appropriate resource allocation decisions and provide high-quality and efficient health care*

THE EVIDENCE

1) Evidence based Medecine…

Literature Search Strategy

Systematic Qualitative Review

- Determine question
- Determine eligibility criteria
  - Population, intervention, comparator, outcome
- Literature search Medline, Embase
- Selection of Studies
  - Independent reviewers
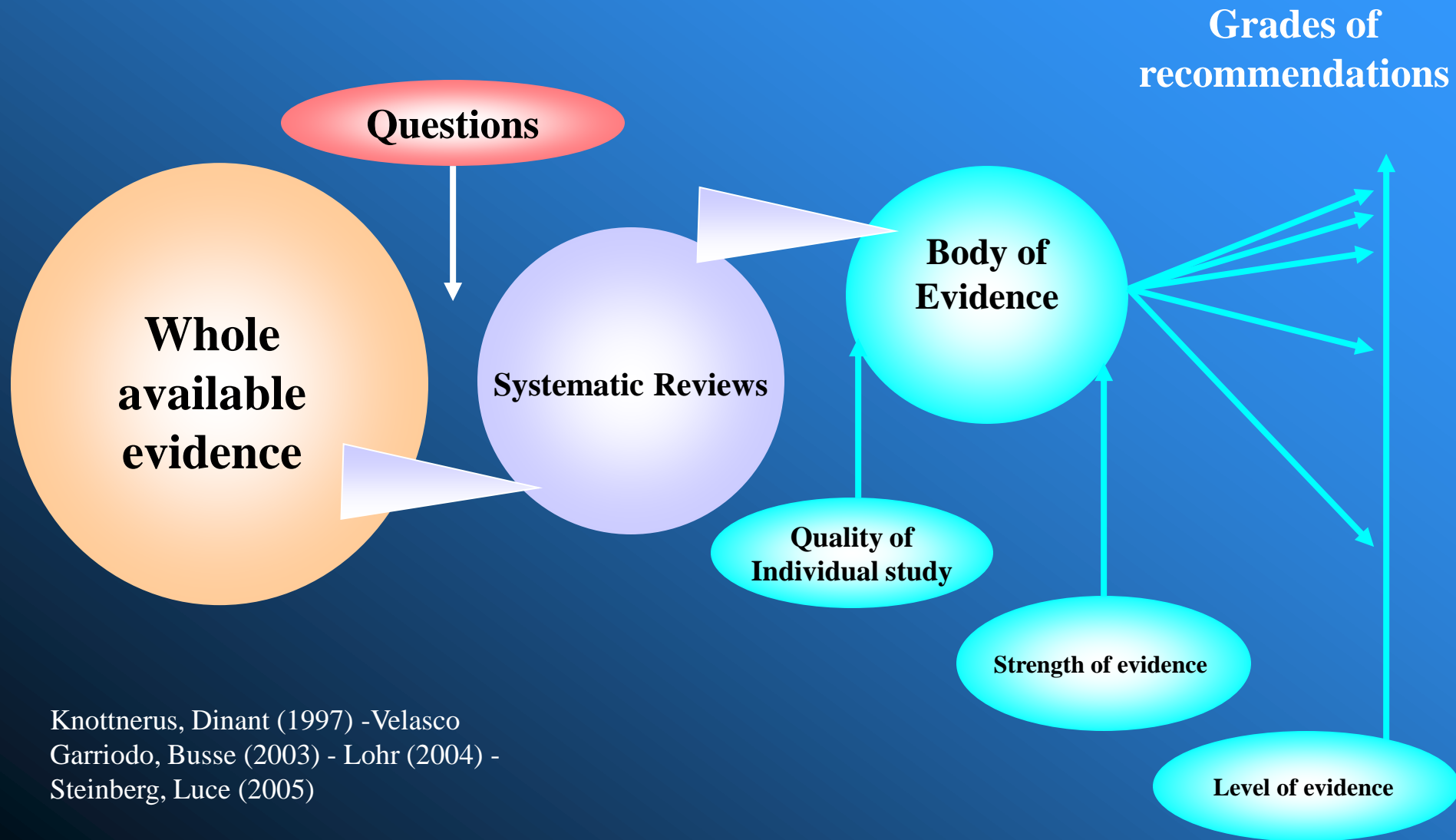- Critical appraisal
  - Quality assessment

Data Extraction

- Evidence tables

IF APPROPRIATE – Quantitative MA

- Statistical pooling
- Heterogeneity
- Bias

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 shoud be avoided

Effect Size

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

2) Types of Designs and Bias…
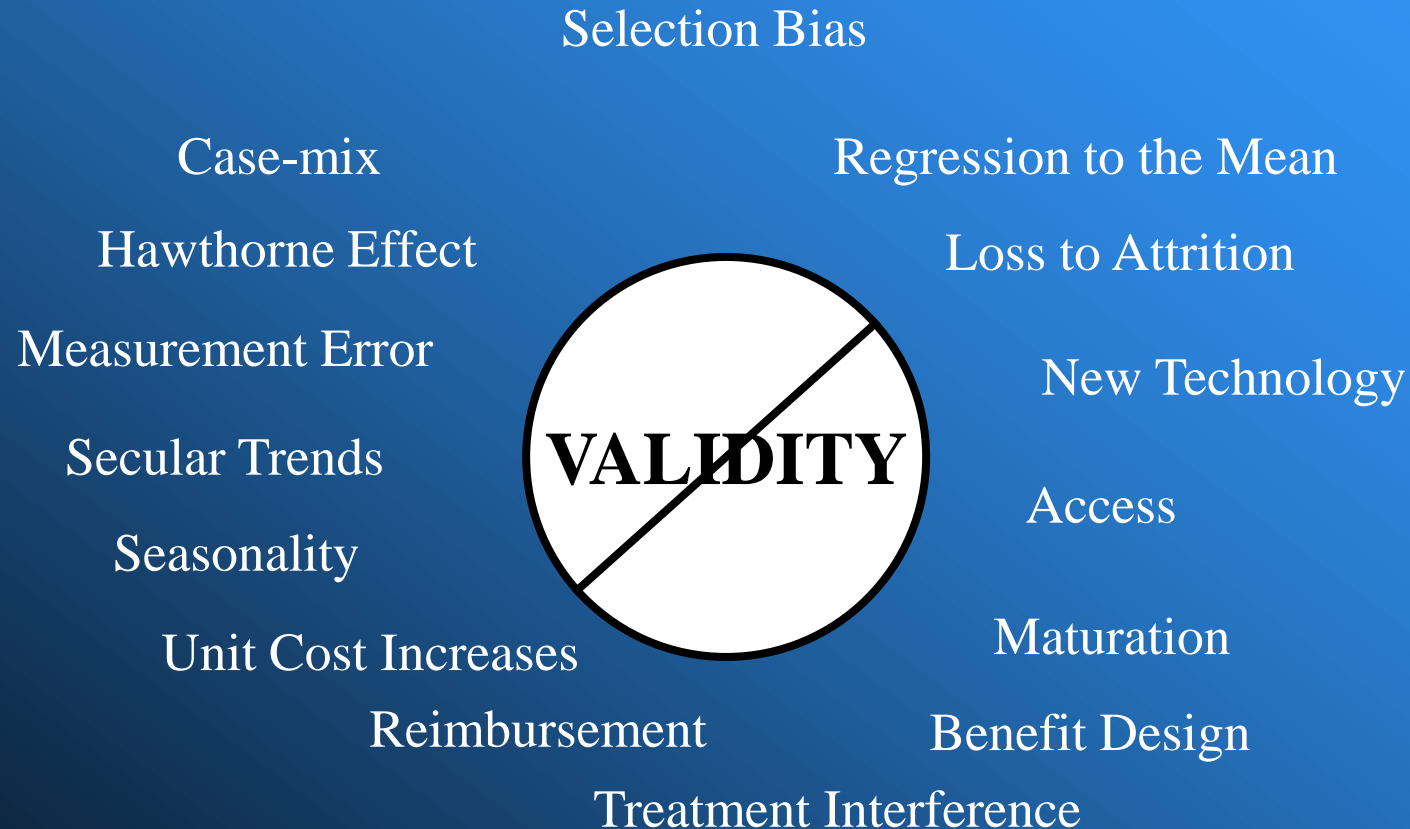
The Ideal Study

- **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   **VALIDITY**

Seasonality   Access

Unit Cost Increases   Maturation

Reimbursement   Benefit Design

Treatment Interference

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

| Greatest Suitability |
| Moderate Suitability |
| Least Suitability |
| Non Suitable |

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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- *TRANSLATING ANALYSIS INTO POLICY*

THE METRICS

1) Measures of Clinical Outcomes

Measures of Clinical Outcomes

- Absolute Risk Reduction
  - The difference in risk of a disease or event between a control group and a treatment group
  - **ARR = (events in treatment group) – (events in control group)**
- Relative Risk Reduction
  - **RRR = 1-[events in treatment group / events in control group]**
- Number Needed to Treat (NNT)
  - The number of patients who would need to receive a treatment in order to prevent or avoid one clinical event A smaller NNT corresponds to higher effectiveness for a therapy
  - **NNT = 1/ARR**

Absolute Risk Reduction (ARR)

- $RD = R_T - R_C$

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

$RAR = 0{,}25 - 0{,}32 = -0{,}07$

- No effect $RD = 0$

Relative Risk Reduction (RRR)

- $RR = R_T / R_C$

	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

$$RRR = 1 - 0,79 = 21\ \%$$

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

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) Measures of Heath Related Quality of Life HRQL

Patient Reported Outcomes

- Definition of health (by World Health Organization, 1948)
  - "Not merely the absence of disease, but complete physical, psychological, and social well-being."
- Assessments
  - Health-related Quality of Life (HRQL)
  - Satisfaction
  - Discomfort or bother
  - Symptom assessment
- Challenge
  - "The challenge for scale developers is to demonstrate that a new application of a PRO instrument adds clinically relevevant information above and beyond that produced by more traditional measures."

HRQL Measures - Instruments

- General or generic instruments
  - Health Profiles
    - SF-36
    - SIP (Sickness Impact Profile)
    - NHP (Nottingham Health Profile)
  - Preference-based Measures
    - QWB (Quality of Well-being)
    - HUI (Health Utility Index)
    - EQ-5D (EuroQol)
- Specific instruments
  - Disease specific
  - Condition/problem specific

Psychometric Validity:
Six Conditions

- Acceptability
- Reliability
- Structural validity
- Clinical validity
- Convergent validity
- Responsiveness

3) Why Consider Costs ?

The Economic Question

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

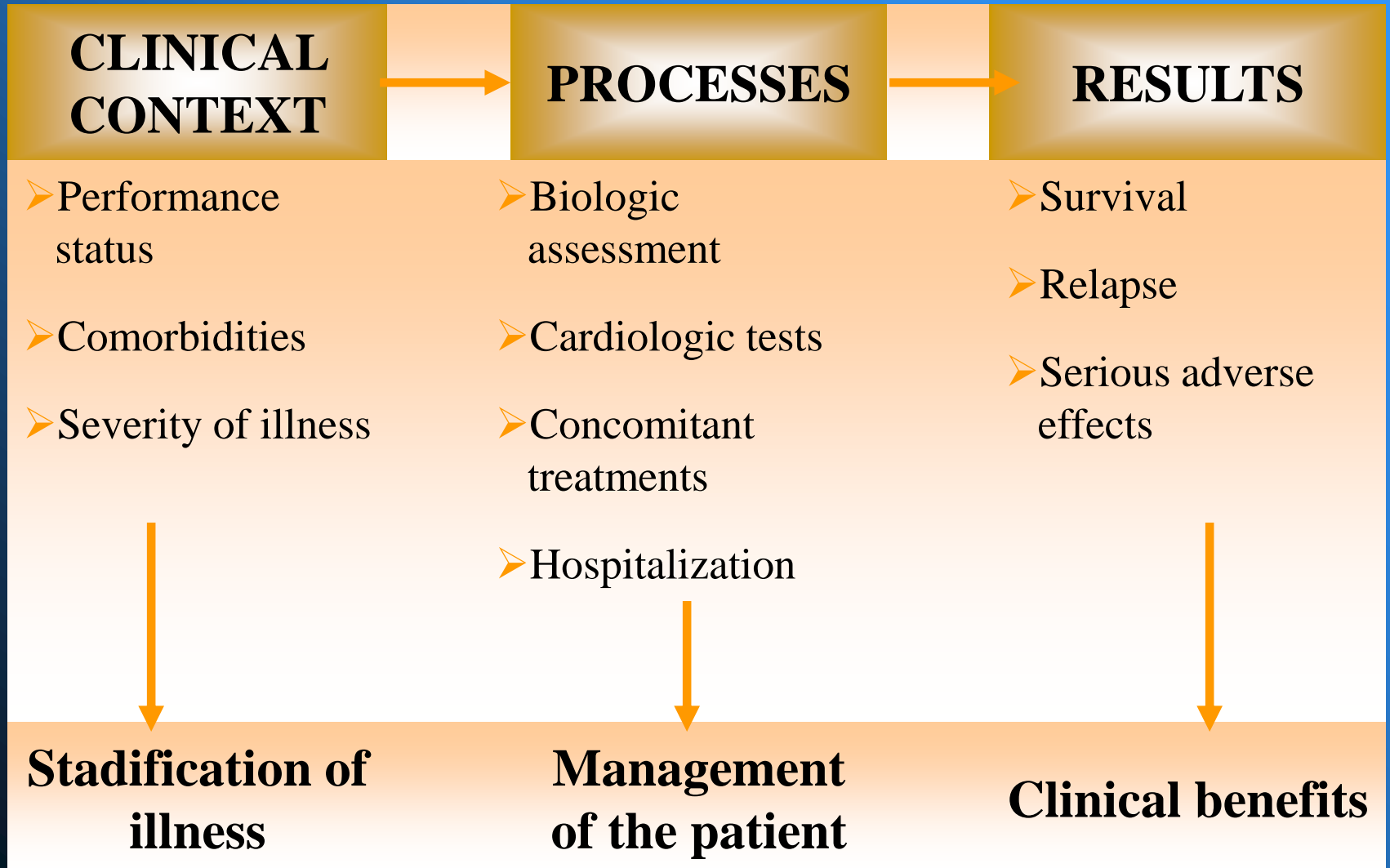Conventional treatment or innovative treatment**?**

The Answer

Choose the treatment which has the highest rate of return on the therapeutic, humanistic and financial aspects of the patient's life, 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
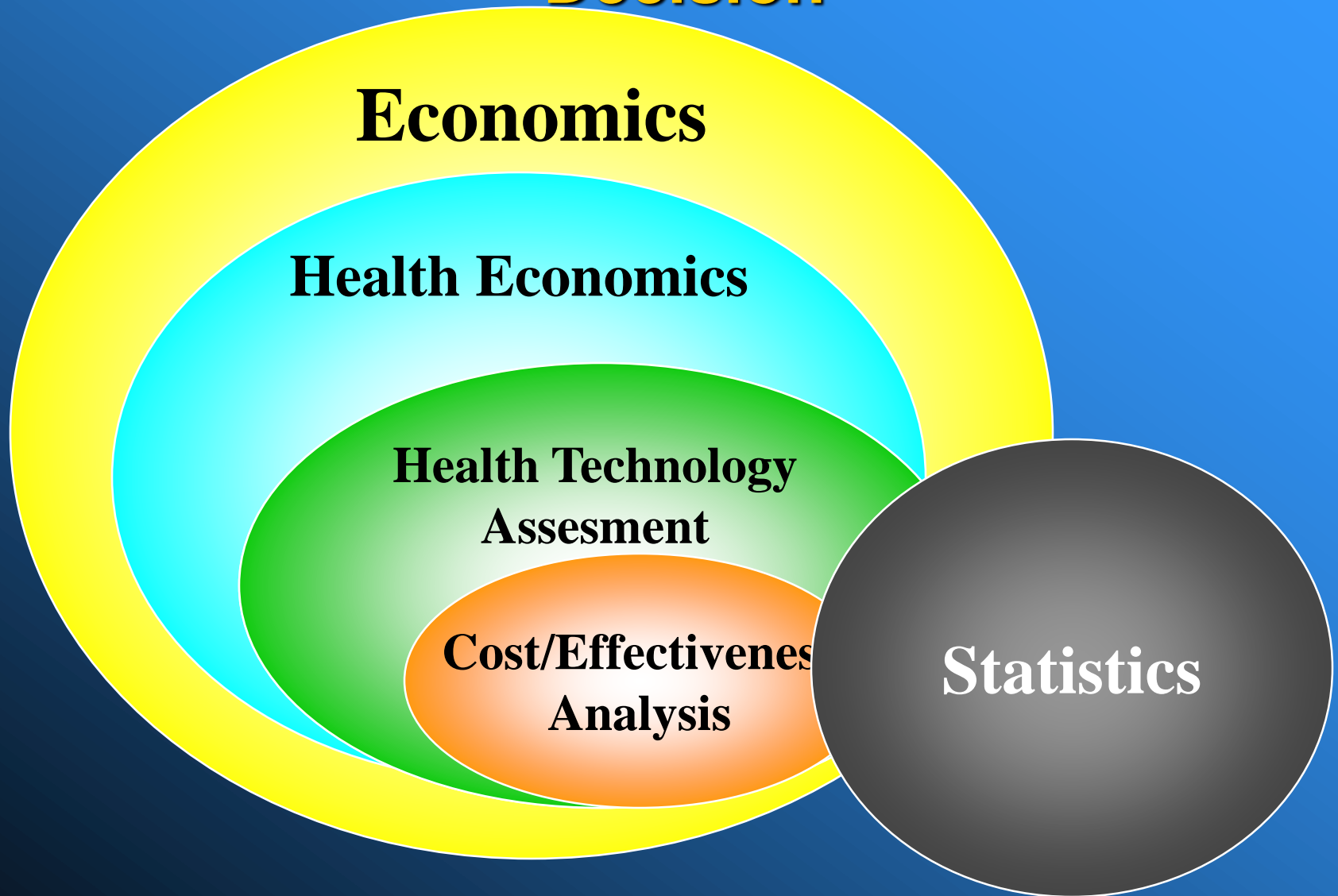- It casts the mould with Euros

Clinical Parameters are Individual and Uncertain Data

CLINICAL CONTEXT	→	PROCESSES	→	RESULTS
➤ Performance status		➤ Biologic assessment		➤ Survival
➤ Comorbidities		➤ Cardiologic tests		➤ Relapse
➤ Severity of illness		➤ Concomitant treatments		➤ Serious adverse effects
		➤ Hospitalization		
↓		↓		↓
Stadification of illness		**Management of the patient**		**Clinical benefits**

Tariffs are Deterministic Variables

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

HTA: The Bridge Between Science and Decision

Economics

Health Economics

Health Technology Assesment

Cost/Effectivenes Analysis

Statistics

4) What Types of Economic Evaluation do we Use in HTA ?

Types of analysis

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

Formulating The Assesment

Are both costs and consequences of the alternatives examined?				
Are two or more alternatives compared?	**NO**			**YES**
	NO	Consequence only	Costs only	**Partial Evaluation**
		Partial Evaluation		
		Outcome description	Cost description	Cost-outcome description
	YES	**Partial Evaluation**		**Full Economic Evaluation**
		Efficacy or effectiveness	Cost analysis	

Burden of Illness

- The first step in establishing the value of a new product
  - **Epidemiology**
    - Quantify the number of individuals affected
  - Estimate the social or patient burden associated with the disease
    - Quality of Life, functional status, patient satisfaction, other patient-reported measures
  - Estimate the economic burden of the disease
    - Cost of illness
- Raise awareness of a disease and identify and establish the unmet needs in the minds of clinicians, payers, and other decision makers

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 Comparative Cost Analysis, which chooses the least expensive alternative regardless of outcomes.

- CMA is also different from "Efficacy Analysis" or "Effectiveness Analysis", which focuses on "outcomes" only.

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 monetary units.

- 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
- 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

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

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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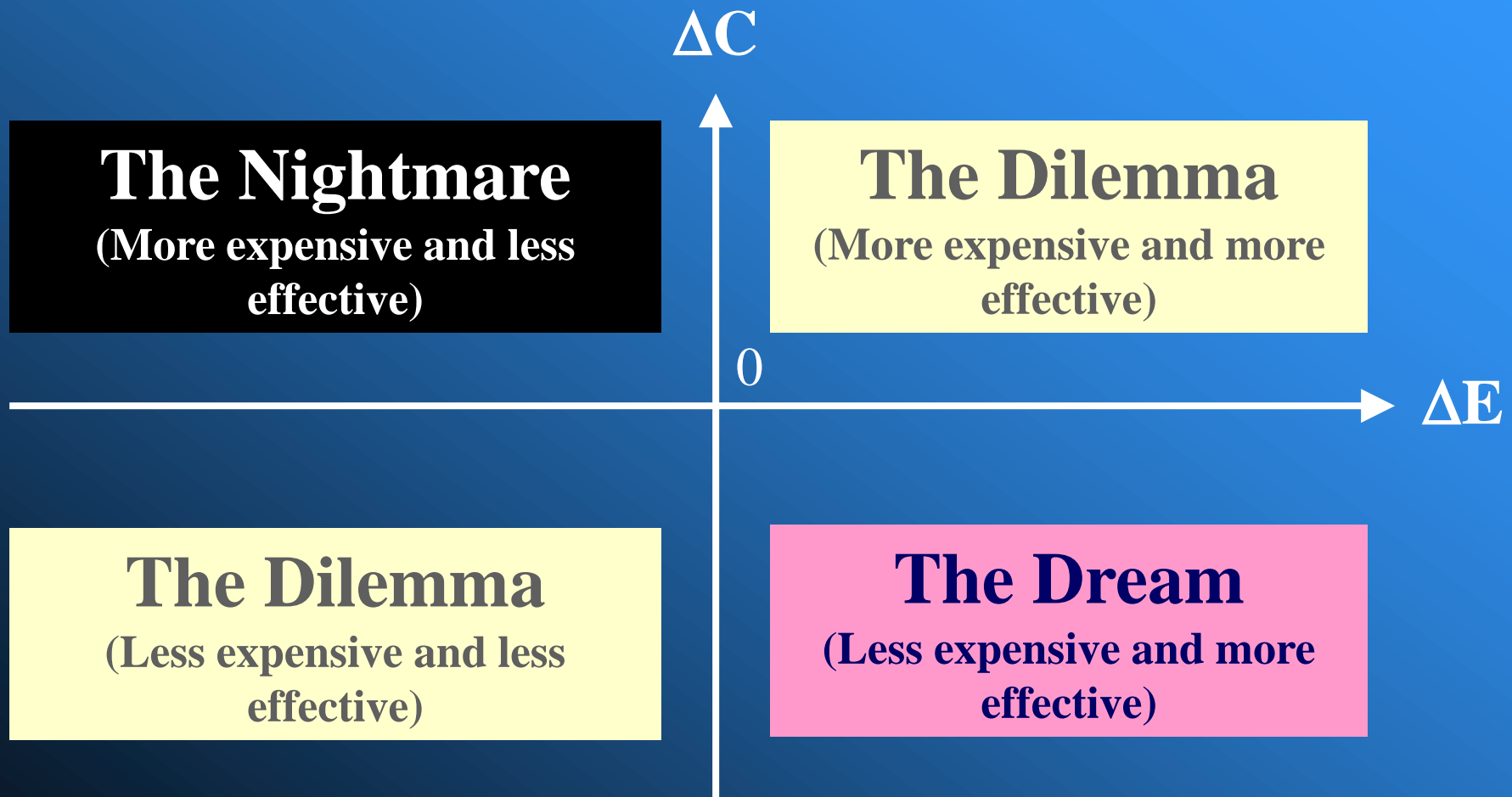 - *Decision criteria under CEA*
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ASSESSMENT CRITERIA

Common End Point

- Cost per life saved (CPLS)
  - Cost required to save one life

- Cost per life year gained (CPYLG)
  - Cost required to save one life divided by number of remaining years of life.

- Cost per Quality Adjusted Life-year (QALY)
  - Cost required to save one life divided by the number of remaining years of life at full health.

Ranking Treatments According to Their Incremental Cost-Effectiveness Ratio

ΔC

The Nightmare
(More expensive and less effective)

The Dilemma
(More expensive and more effective)

0

ΔE

The Dilemma
(Less expensive and less effective)

The Dream
(Less expensive and more effective)

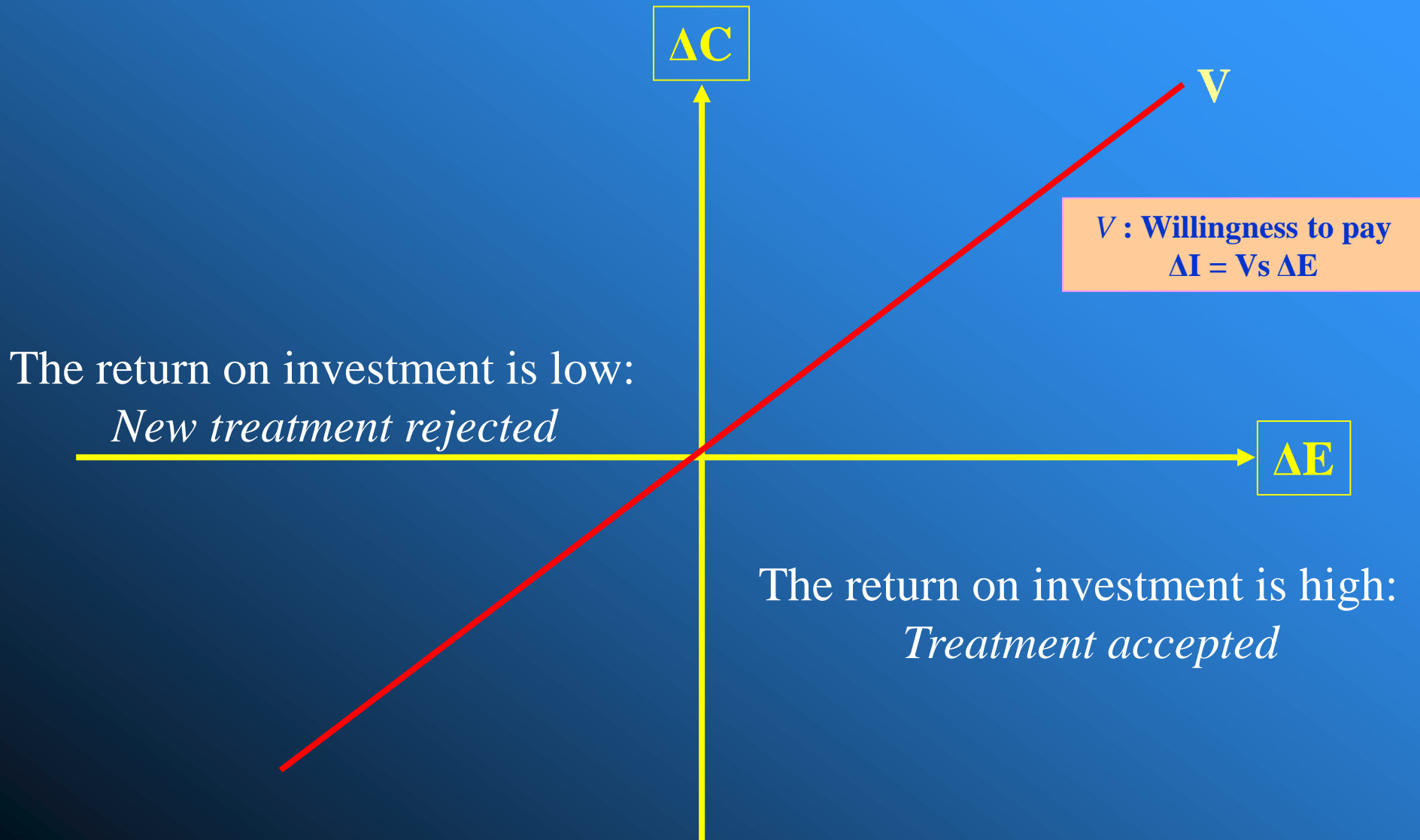# How to Decide If
The Outcomes are Worth the Effort ?

Two possible reference criteria:

- **MARGINAL WILLINGNESS TO PAY: the maximum 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**
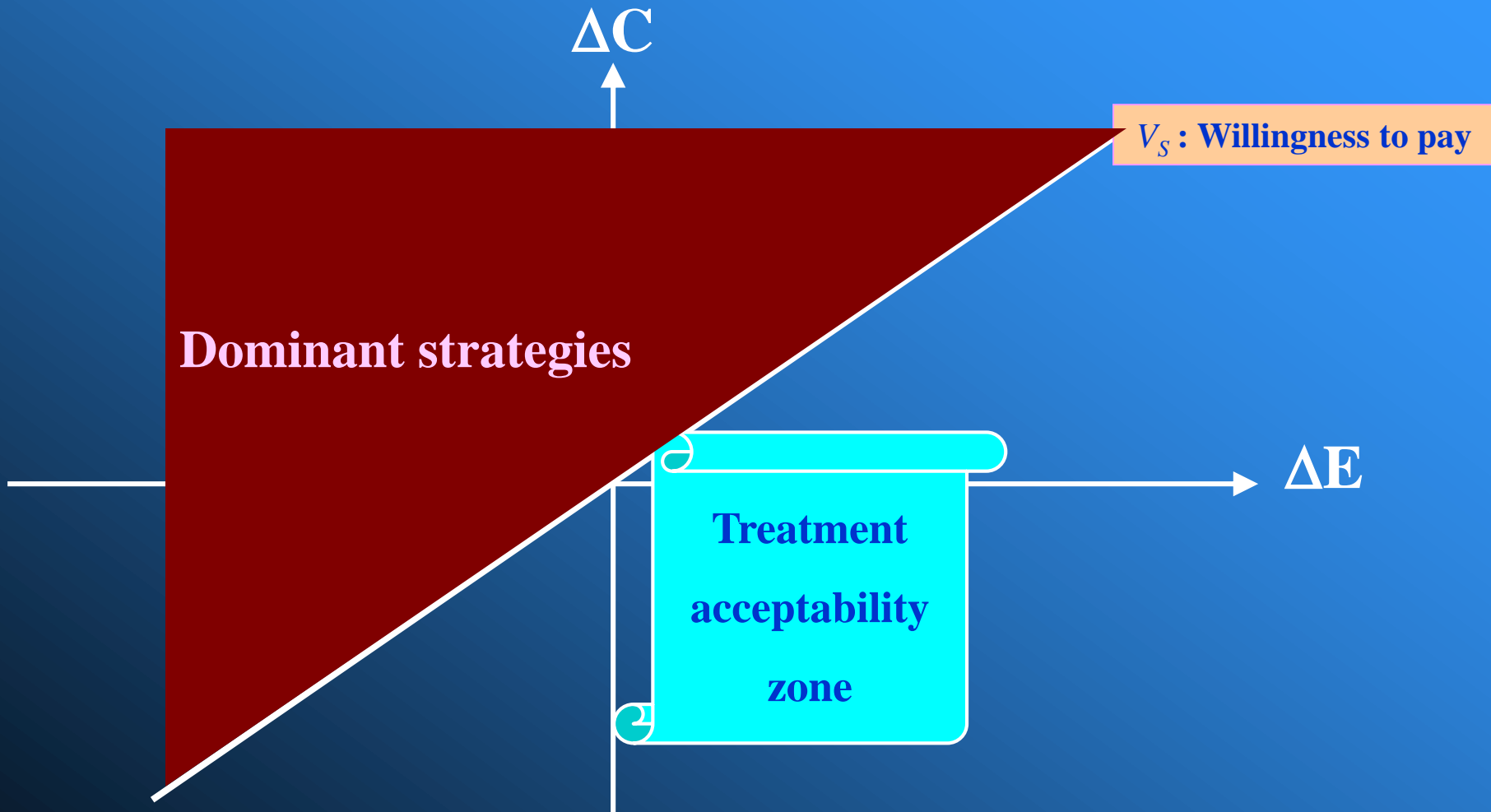
Making Decisions Using ICER

- If the ICER doesn't fall into the quadrant of dominated or dominating strategy, then decision makings based on CE-ratio become a bit tricky.

- Rule 1: value judgement specified by an organization
  - $30,000 per QALY used in NICE guidelines

- Problems?

Limits of Solidarity

$$\Delta C$$

V

V : **Willingness to pay**
$$\Delta I = Vs\ \Delta E$$

The return on investment is low:
New treatment rejected

$$\Delta E$$

The return on investment is high:
Treatment accepted

How Much are the « Fit » Willing to Pay?

ΔC

V_S : **Willingness to pay**

Dominant strategies

ΔE
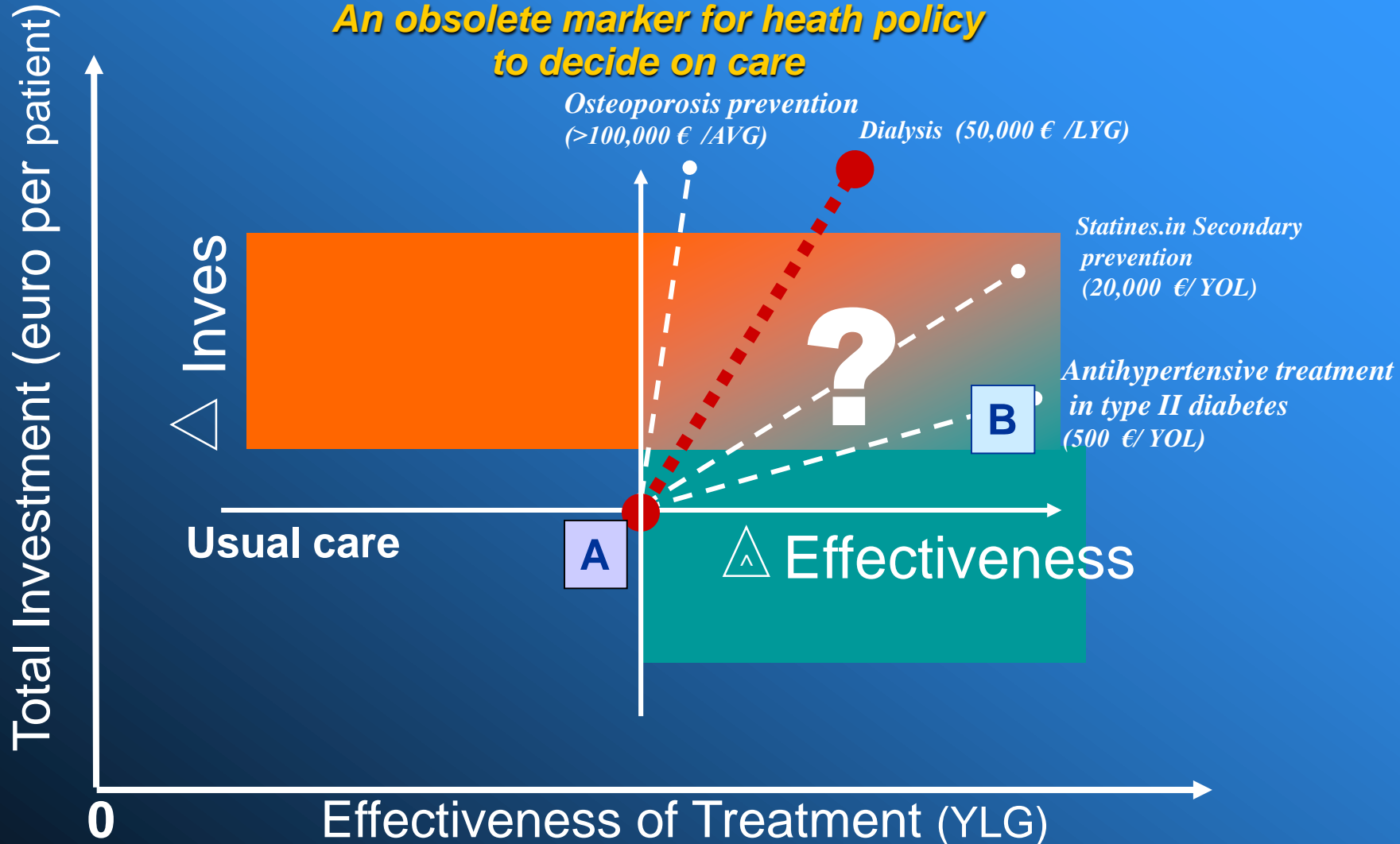
Treatment acceptability zone

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?

Threshold :
30 - 50,000 € per Year of Life Saved
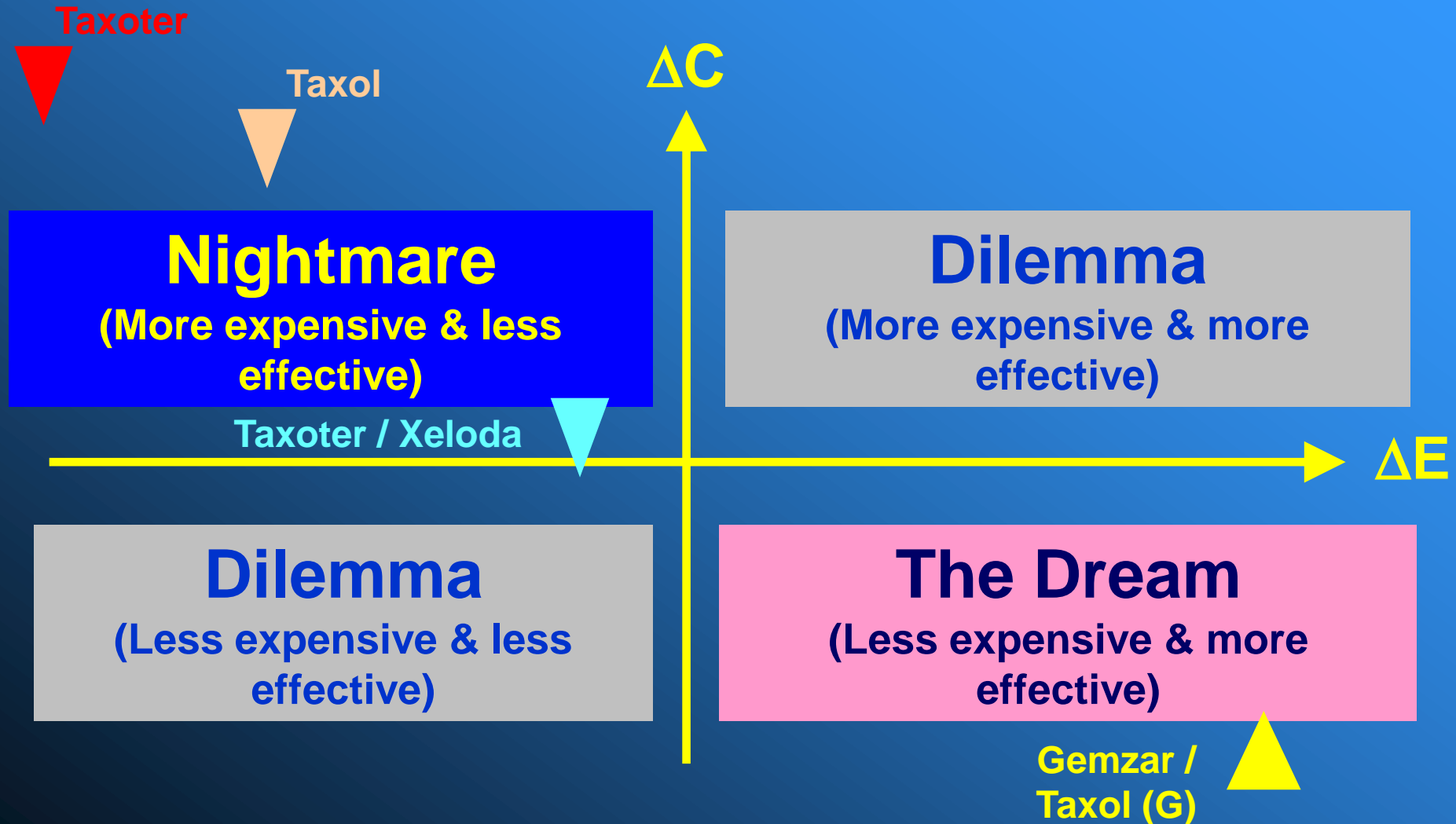
*An obsolete marker for heath policy
to decide on care*

*Osteoporosis prevention
(>100,000 € /AVG)*

Dialysis (50,000 € /LYG)

*Statines.in Secondary
prevention
(20,000 €/ YOL)*

*Antihypertensive treatment
in type II diabetes
(500 €/ YOL)*

Total Investment (euro per patient)

△ Inves

?

B

Usual care

A

△ Effectiveness

0   Effectiveness of Treatment (YLG)

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

League Table Example

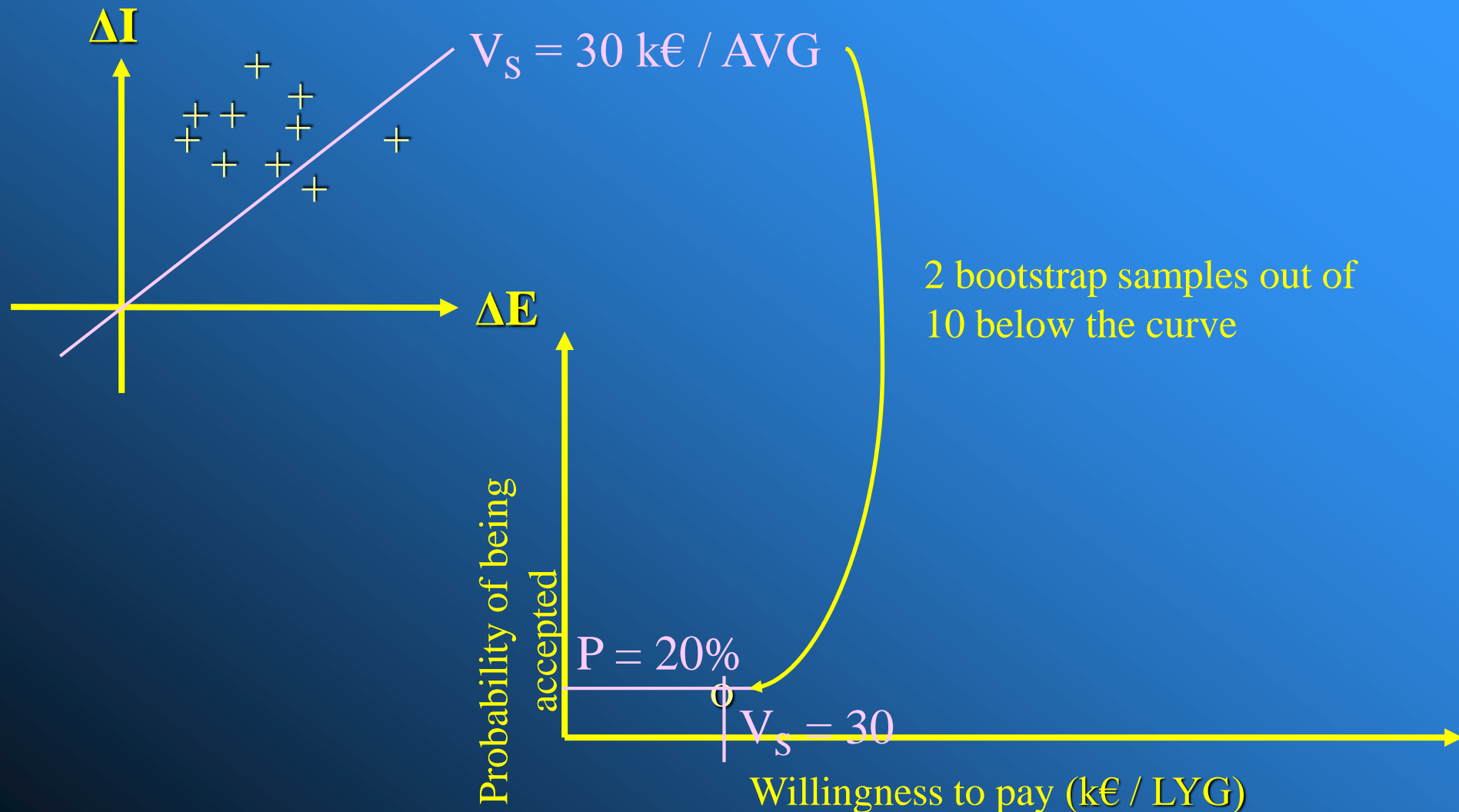| Treatment	$ QALY
Coronary artery bypass surgery for left main coronary artery	$ 4,200
Treatment of severe hypertension in males age 40	$ 9,400
Treatment of mild hypertension in males age 40	$ 19,100
Estrogen therapy for postmenopausal symptoms	$ 27,000
Hospital dialysis	$ 54,000

An Example in Metastatic Breast Cancer

Taxoter

Taxol

ΔC

Nightmare
(More expensive & less effective)

Taxoter / Xeloda

Dilemma
(More expensive & more effective)

ΔE

Dilemma
(Less expensive & less effective)

The Dream
(Less expensive & more effective)
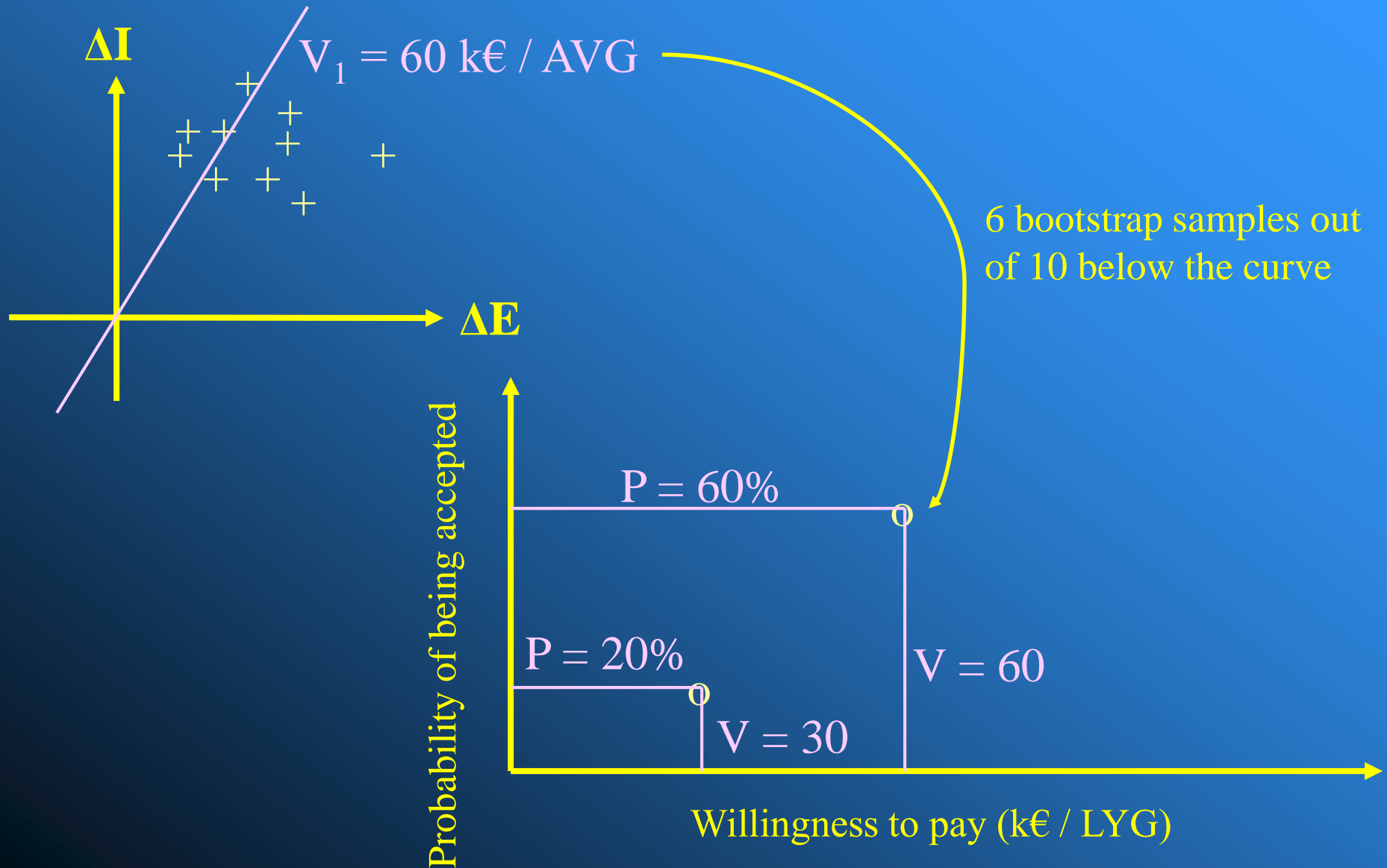
Gemzar / Taxol (G)

A Need: To Take Hold of the Uncertainty Inherent to the Rules of the Game

- The value (V) given by the Society to an additional unit of effect is a **socio-political value** which the evaluator cannot judge.

- The results must be analysed in light of the different **possible willingness to pay** from the purchaser by constructing an acceptability curve for the treatment by the statutory authorities.

- This curve shows the probability that this treatment will considered to be **efficient** by the authorities for all possible values of V.

- **Estimation procedure**: generation of ∆E, ∆C couples bootstrap – by the proportion of points beneath the line for all values of Vs .

Acceptability for Reimbursement by the Legal Authorities,
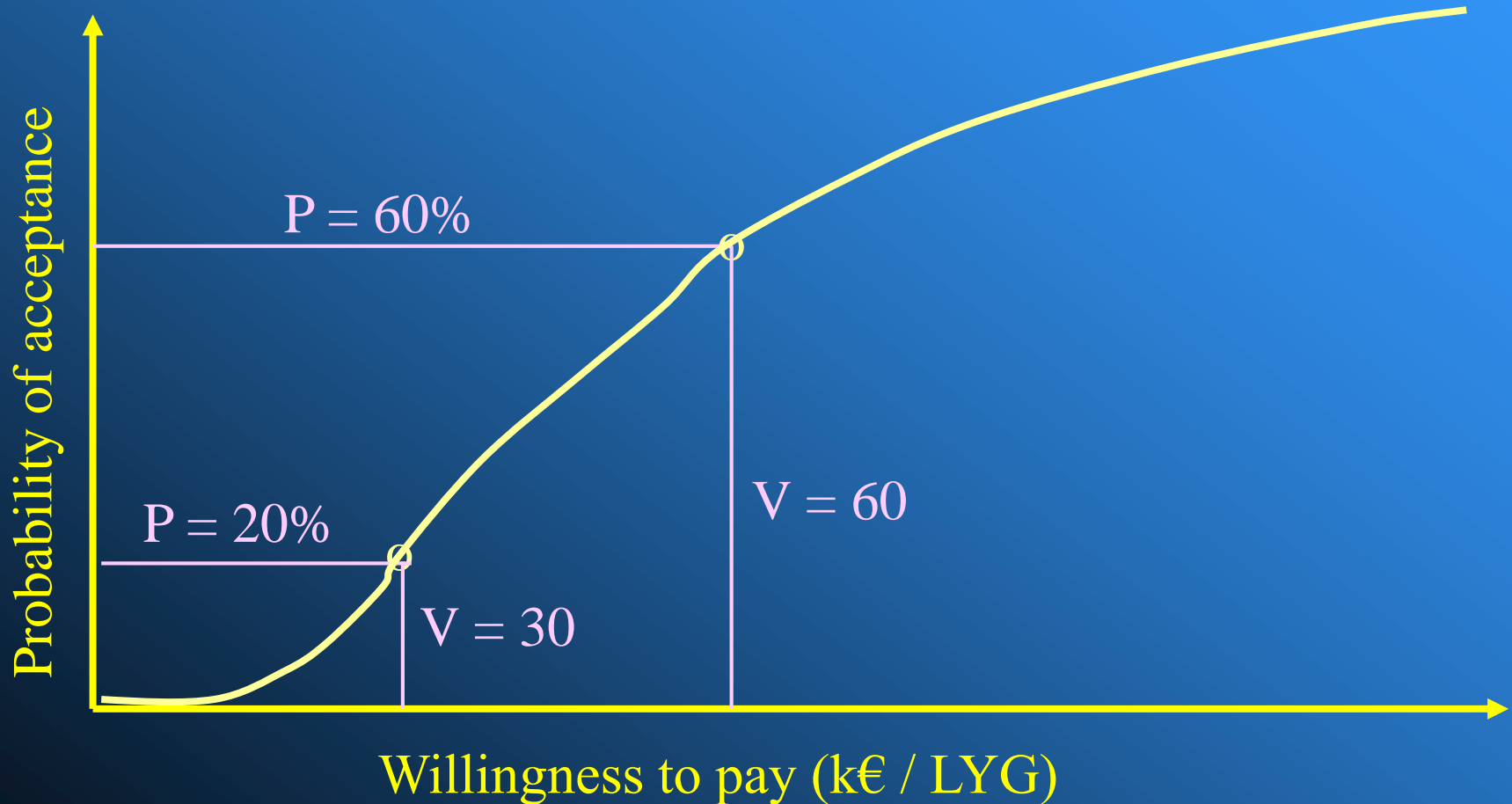## *depending on the financial effort are willing to employ*

ΔI

$V_S = 30$ k€ / AVG

ΔE

2 bootstrap samples out of 10 below the curve

Probability of being accepted

P = 20%

$V_s = 30$

Willingness to pay (k€ / LYG)

Acceptability for Reimbursement by the Legal Authorities,
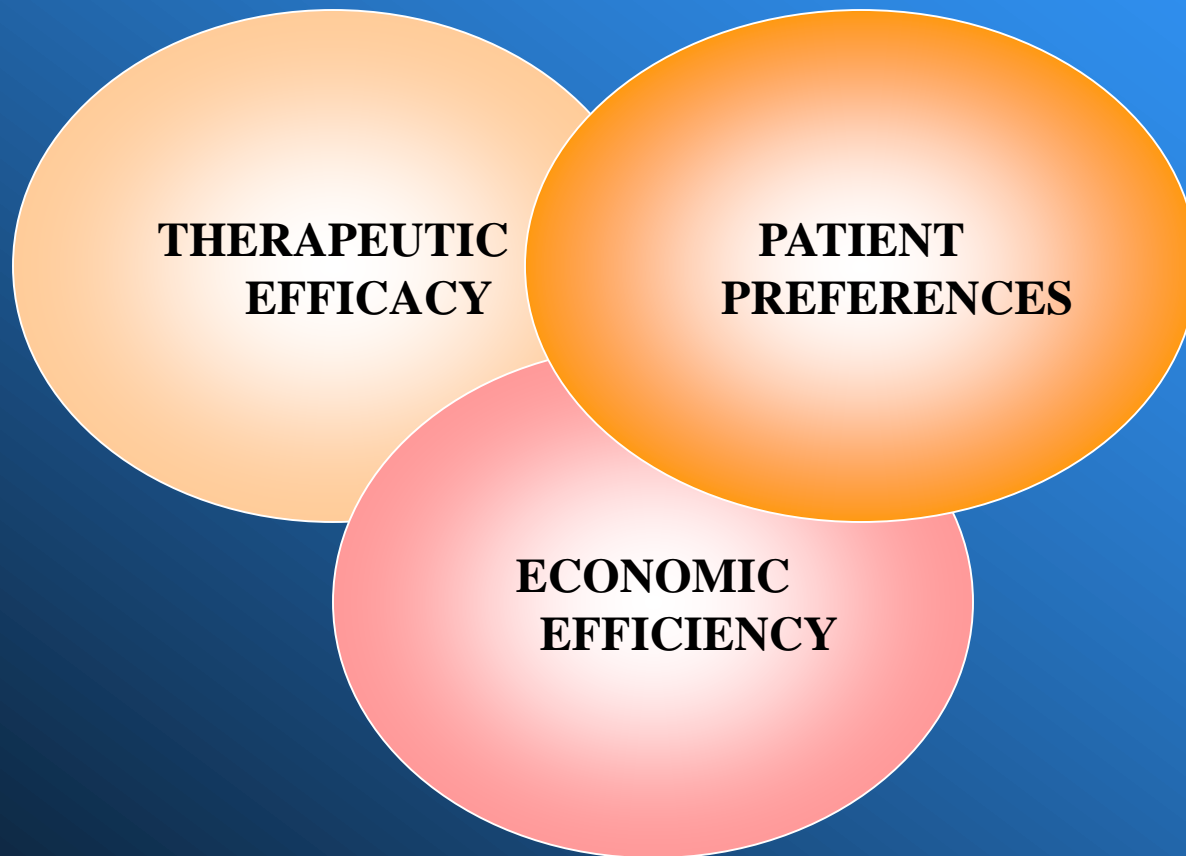*depending on the financial effort are willing to employ*

ΔI

$V_1 = 60\ k€ / AVG$

ΔE

6 bootstrap samples out of 10 below the curve

Probability of being accepted

P = 60%

P = 20%

V = 60

V = 30

Willingness to pay (k€ / LYG)

Reimbursement Acceptability Curve for the Statutory Authorities:
A coherent tool for the public bodies

Probability of acceptance

P = 60%

P = 20%

V = 60

V = 30

Willingness to pay (k€ / LYG)

4) Translating Analysis into Policy

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

THERAPEUTIC EFFICACY

PATIENT PREFERENCES

ECONOMIC EFFICIENCY

Generalised Review of Probing Data

RCTs · Comparative Trial · Cohort · Miror Study · Clinical practice

Expert Advice

Review

Quality of life · Decisional Meta analysis · Investment

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

- To structure the information in a single analytical framework

- To integrate simultaneously benefits, risks and costs

- To estimate quantitatively 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

Dissemination of Results

- Highly dynamic process
- Susceptible to:
  - Surprises
    - In the evolving application of technology
  - Uncertainties
    - In interpretation and extrapolation of evidence
  - Value Judgments
    - As policymakers consult evidence to decide what technologies to cover
- Key stakeholders
  - Consumer groups, media, industry, public and professional considerations

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 monetary unit invested