SERONO Meeting

LUTETIA Hotel, Paris - December 20th, 2002

PharmacoEconomics: a Field Between Clinical Research and Marketing Studies

Professor Robert Launois

REES France : Réseau d 'Evaluation en Economie de la Santé

http://www.rees-france.com

Preamble

The economist is not a bookkeeper. The clinical decision is multifactorial; the economic arguments are only arguments to consider among the others.

The Economic Evaluation

Provides ***Enlightenment*** for

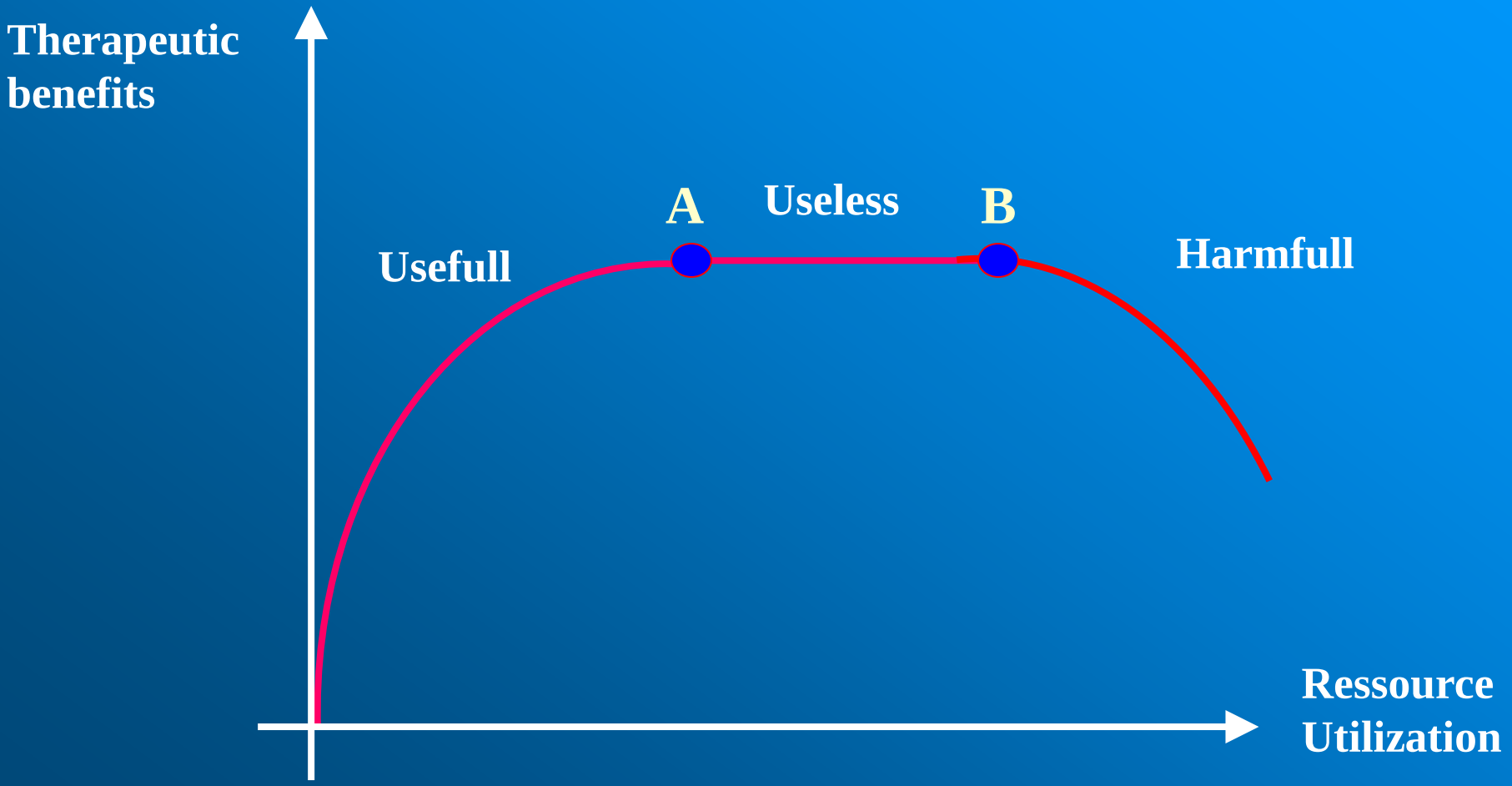
the ***clinician*** and for the ***decision-maker***

WHEN NOT EVERYTHING CAN BE REIMBURSED TO EVERYONE

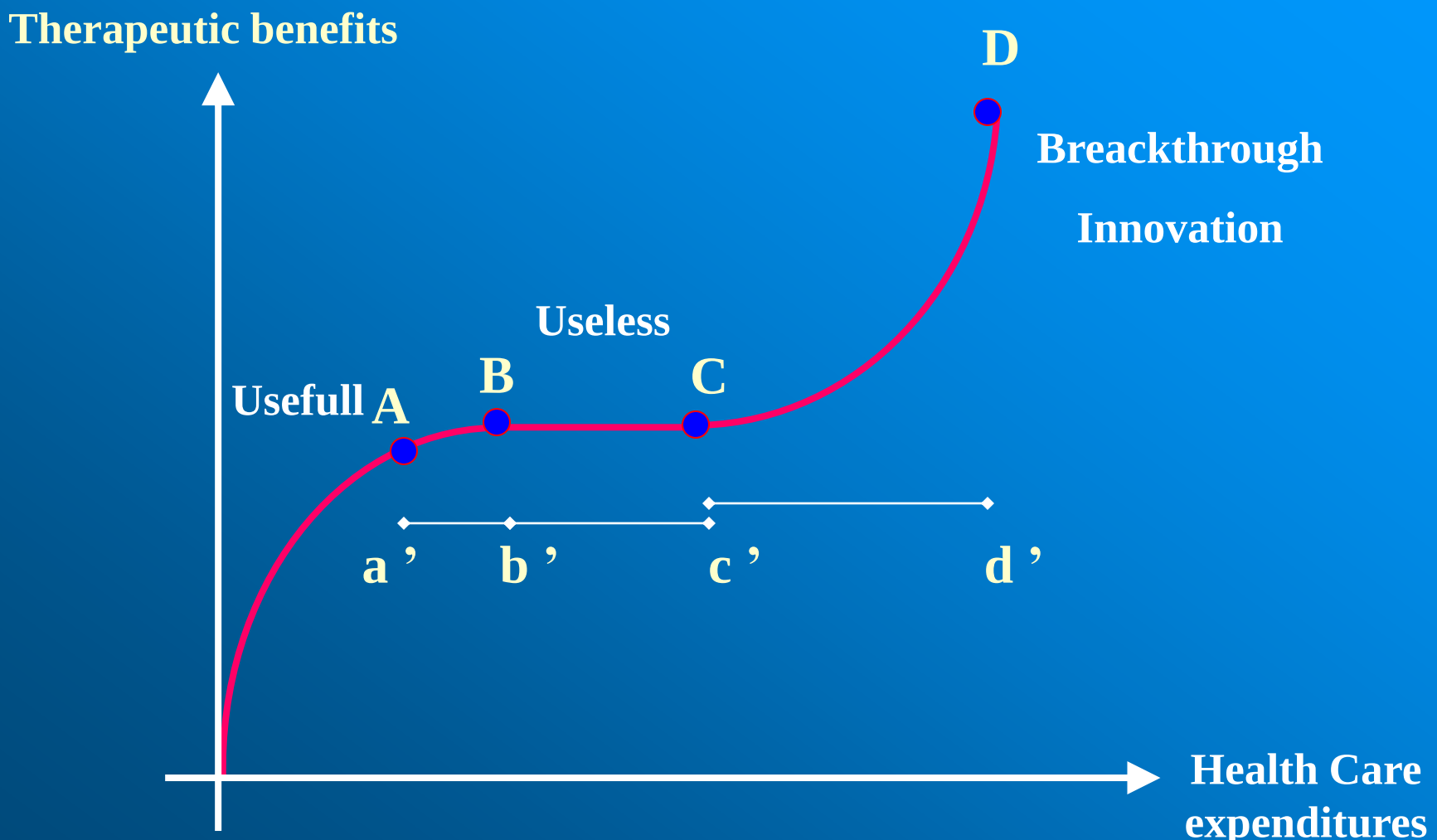
allowing them to study

the economic repercussions of their choices

« Health, a Priceless but Costly Good » :
An Obsolete Slogan



Choices Have To Be Made

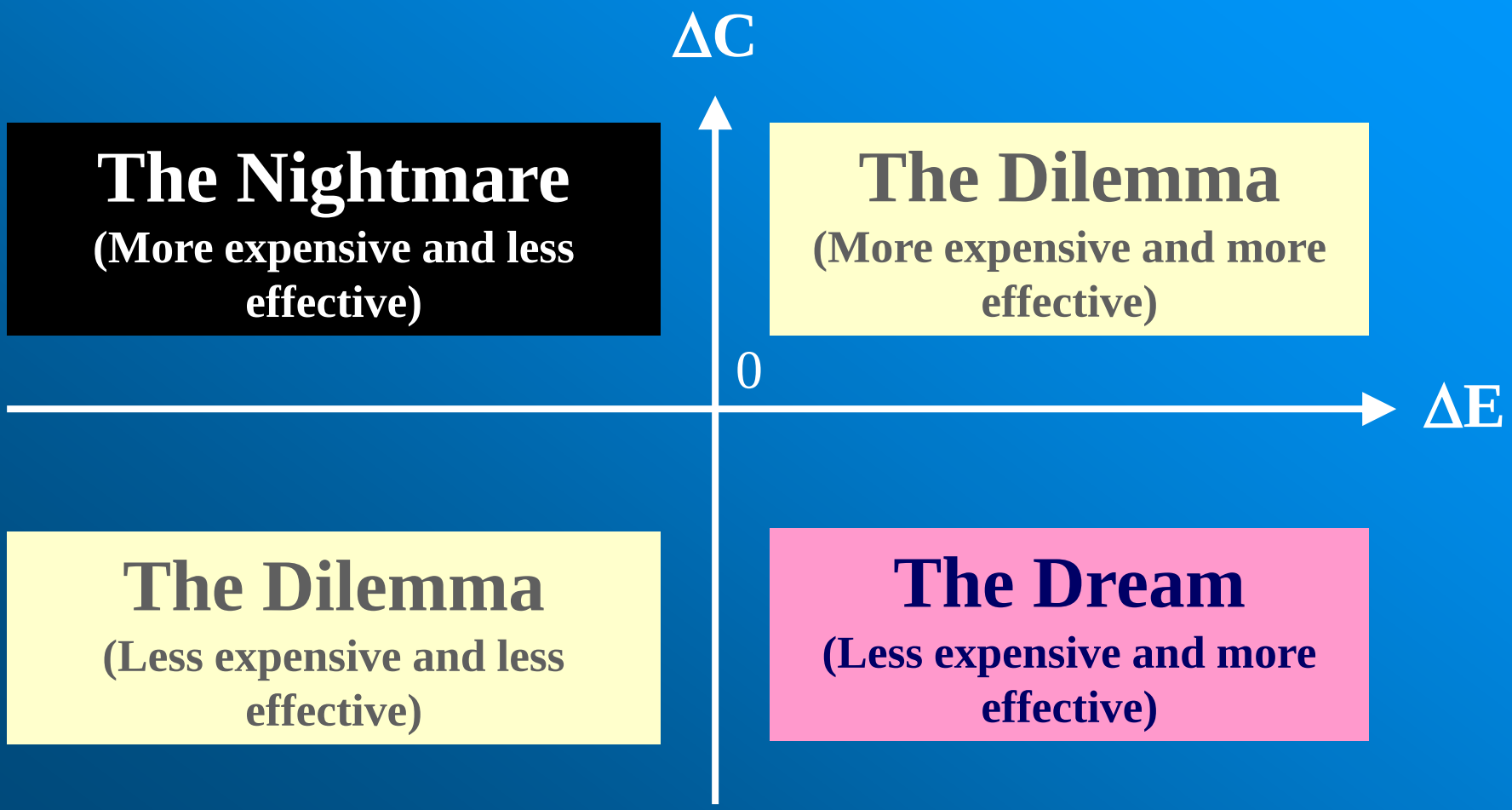


Efficiency…Efficiency…
The Key End Point for the Economist

$$\frac{\Delta C}{\Delta E} = \frac{\Delta Ct + \Delta Cct - \Delta Ccm}{\Delta E}$$

C : Total medical cost per patient treated
E : Total effectiveness
Ct : Cost of treatment
Cct : Cost of complications due to treatment
Ccm : Cost of complications due to morbidity

Ranking of Treatements Based on Their Incremental Cost-Effectiveness Ratio



When Can We Really Refer to An Economic Evaluation?

Is a comparison of costs and results performed systematically?

Is there a control group?

	NO	YES
NO	**NO EVALUATION**	**NO EVALUATION**
YES	**PARTIAL EVALUATION**	**FULL EVALUATION** **Investigation of efficiency**

REES France

The End of a Paradigm:

REES France, Faculty of Medicine - Université Paris XIII - France

launois.rees@wanadoo.fr

http://www.rees-france.com

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 patient to whom it is given ? »
- In clinical practice the question is **effectiveness** « does the drug work in patient to whom it is offered? »

Experimental Models in Laboratory Conditions Are Far Away From the Real World

LEVEL OF EVIDENCE

Randomised clinical trials

EVALUATION's

TARGETS

Patient

Disease

Insured

TREATMENTS

Efficacy
Safety

Quality of Life

Piggy back

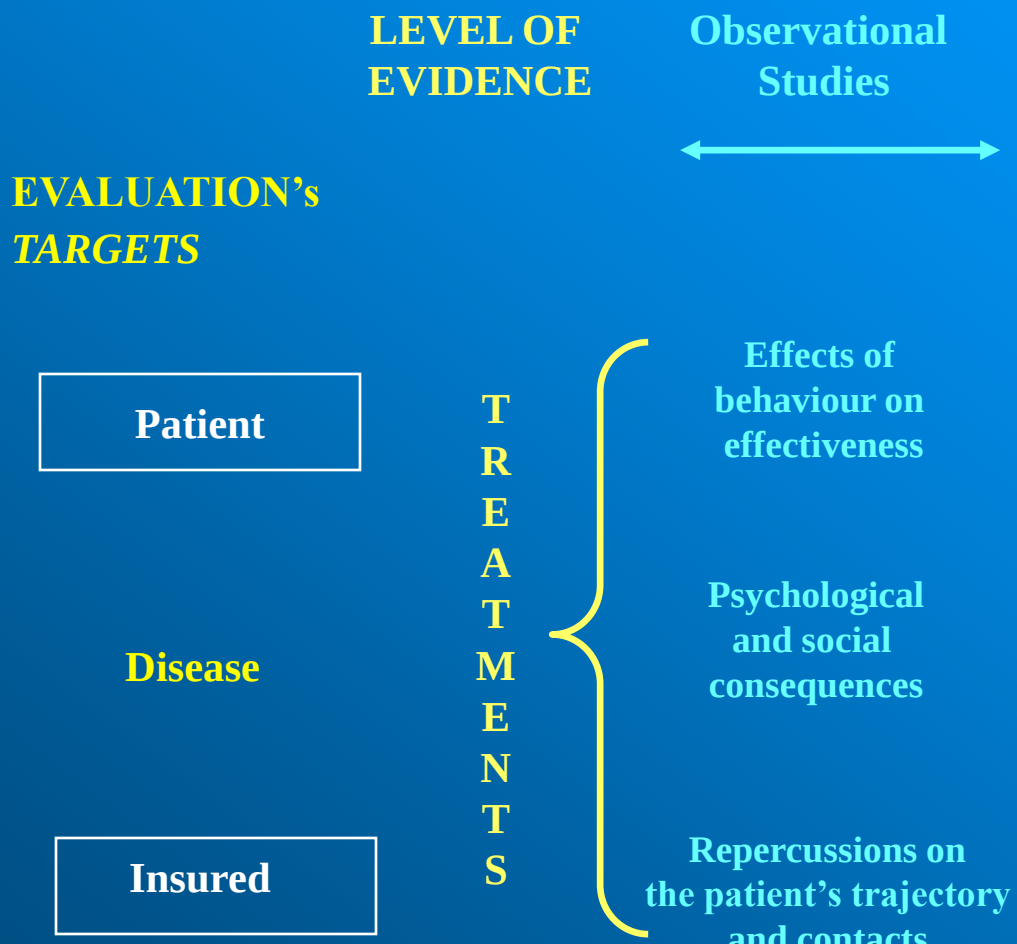
The Results of The RCT's are Limited in their Generalizibility

RCT are conducted under strict protocol-driven conditions with:

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

Observational Studies Assess Impacts

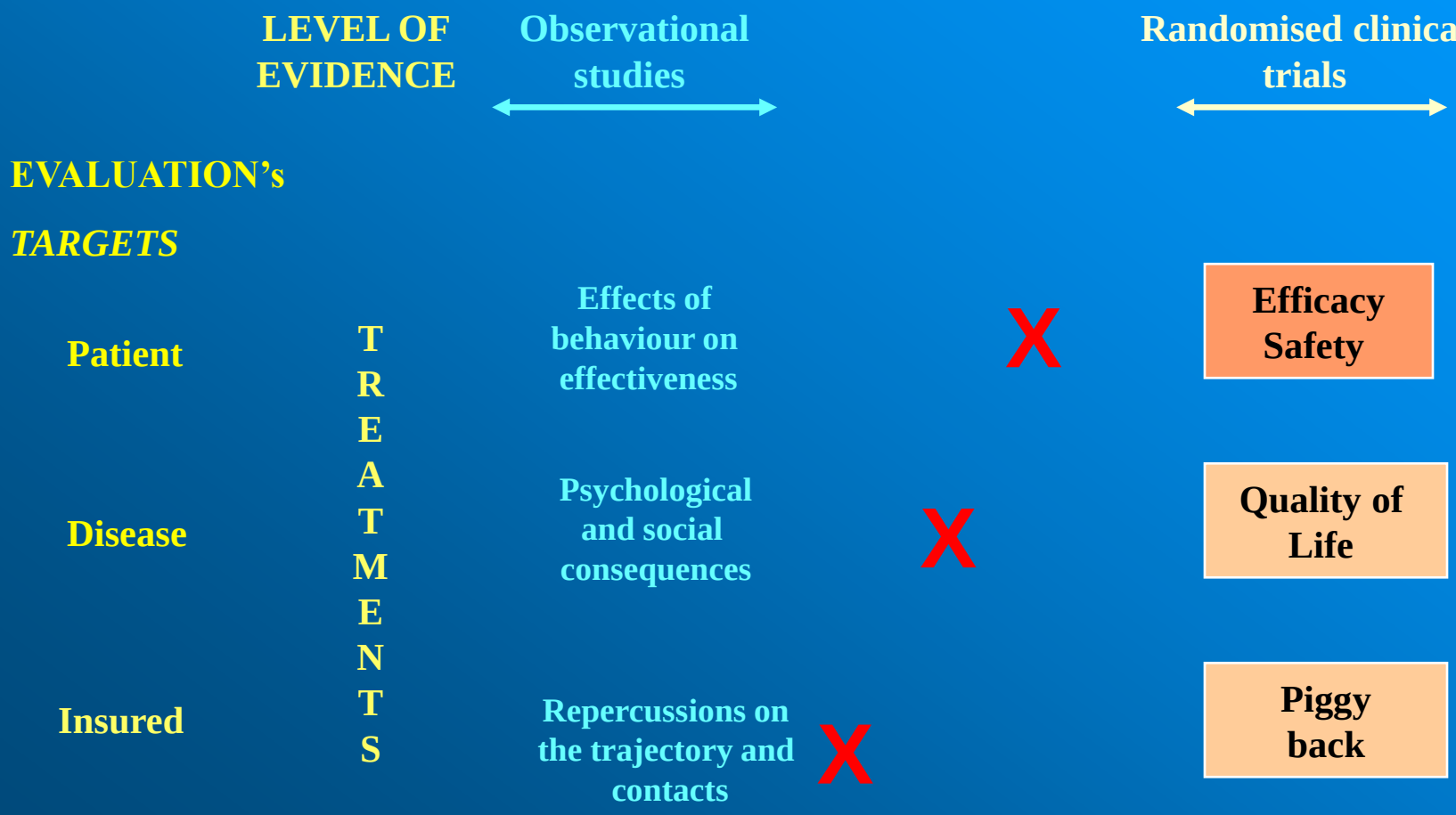
of Individual's Behavioral Decision making Processes on Outcomes



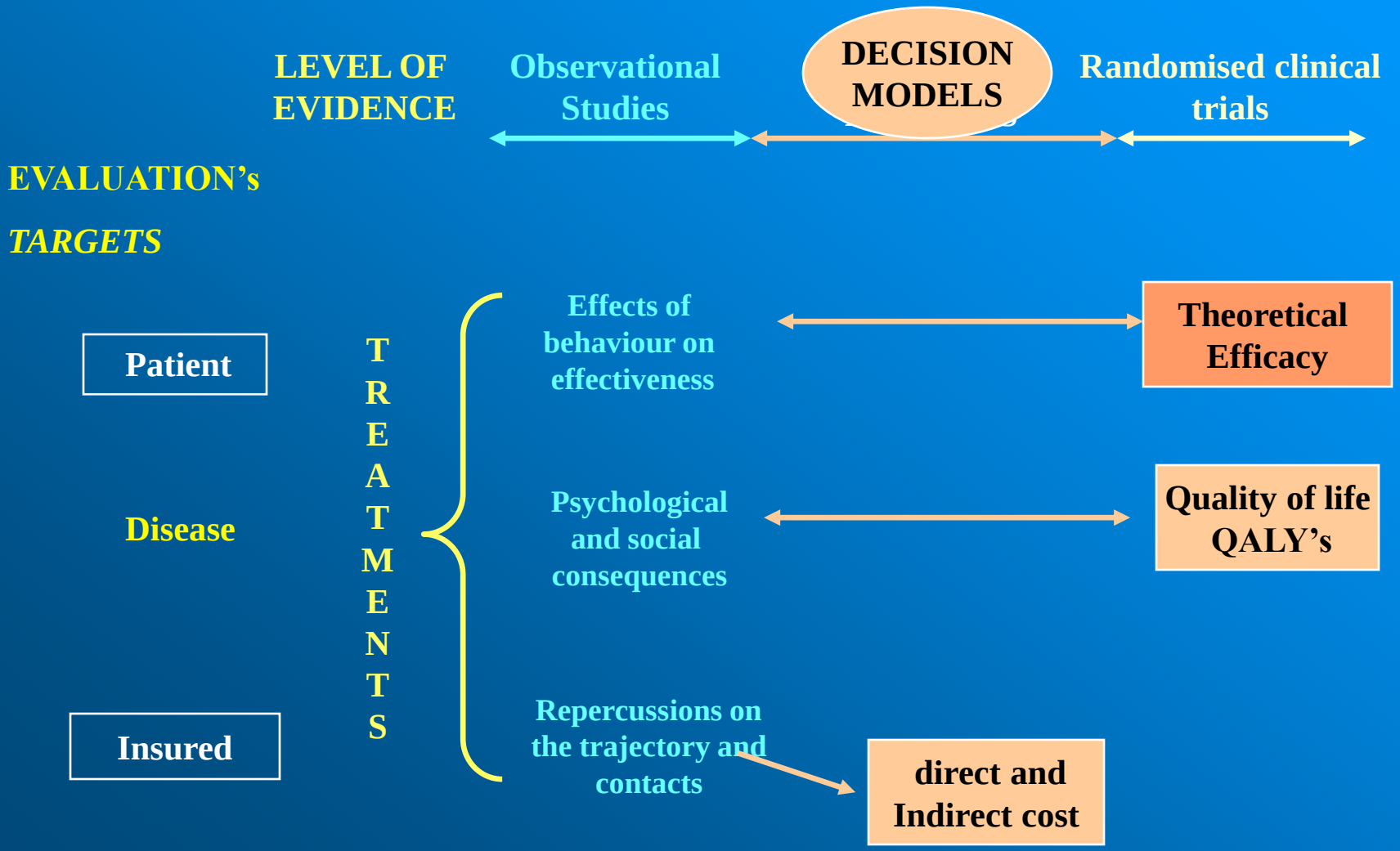
But Without Control, They Only Show the Natural Course of Illness

- 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 Experimental Models and Real Life?

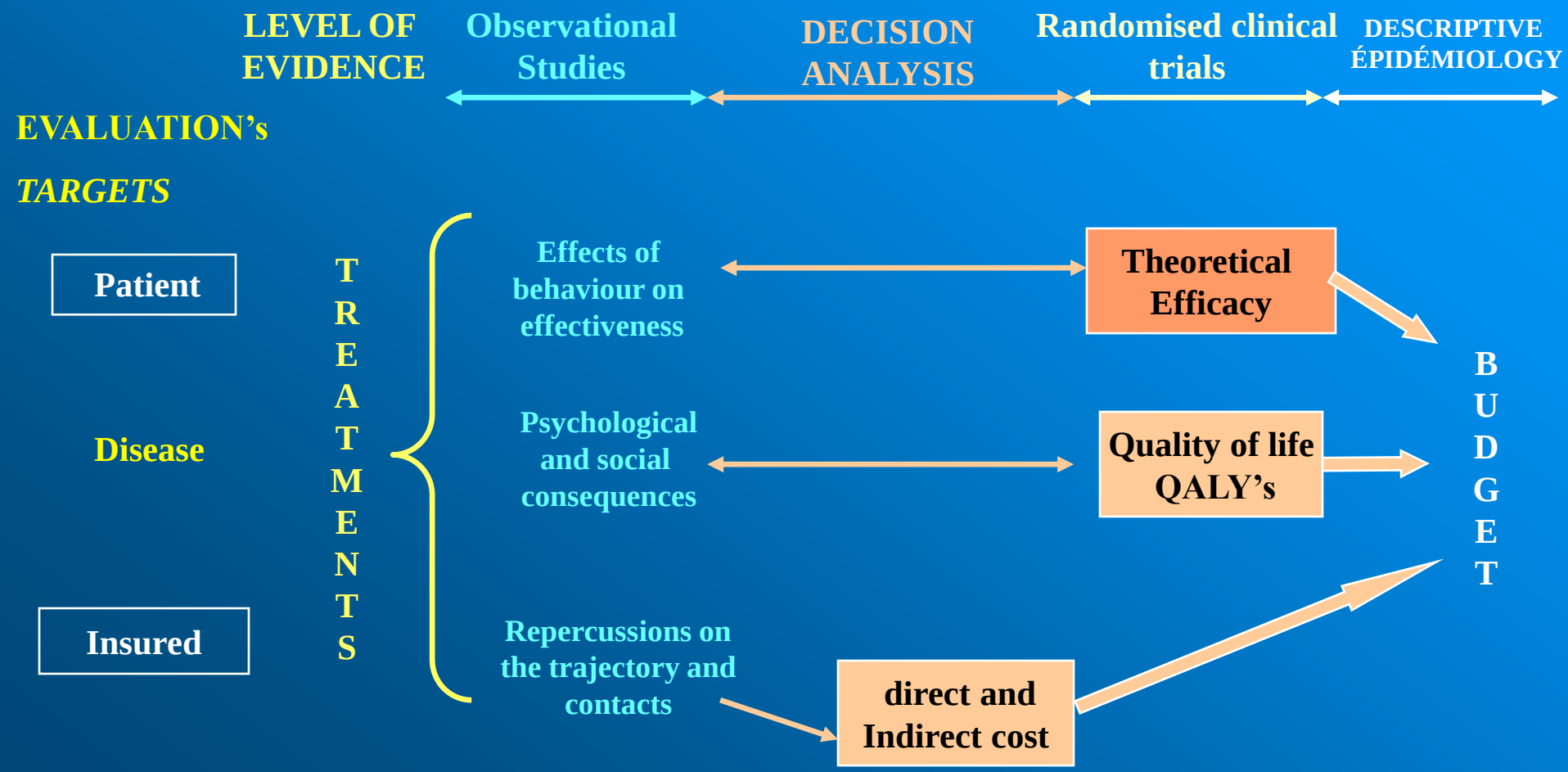


First Attempt : Decision Analysis + …



+ Epidemiological Study ,

Marry RTC's Results with usual pratice patterns



REES France

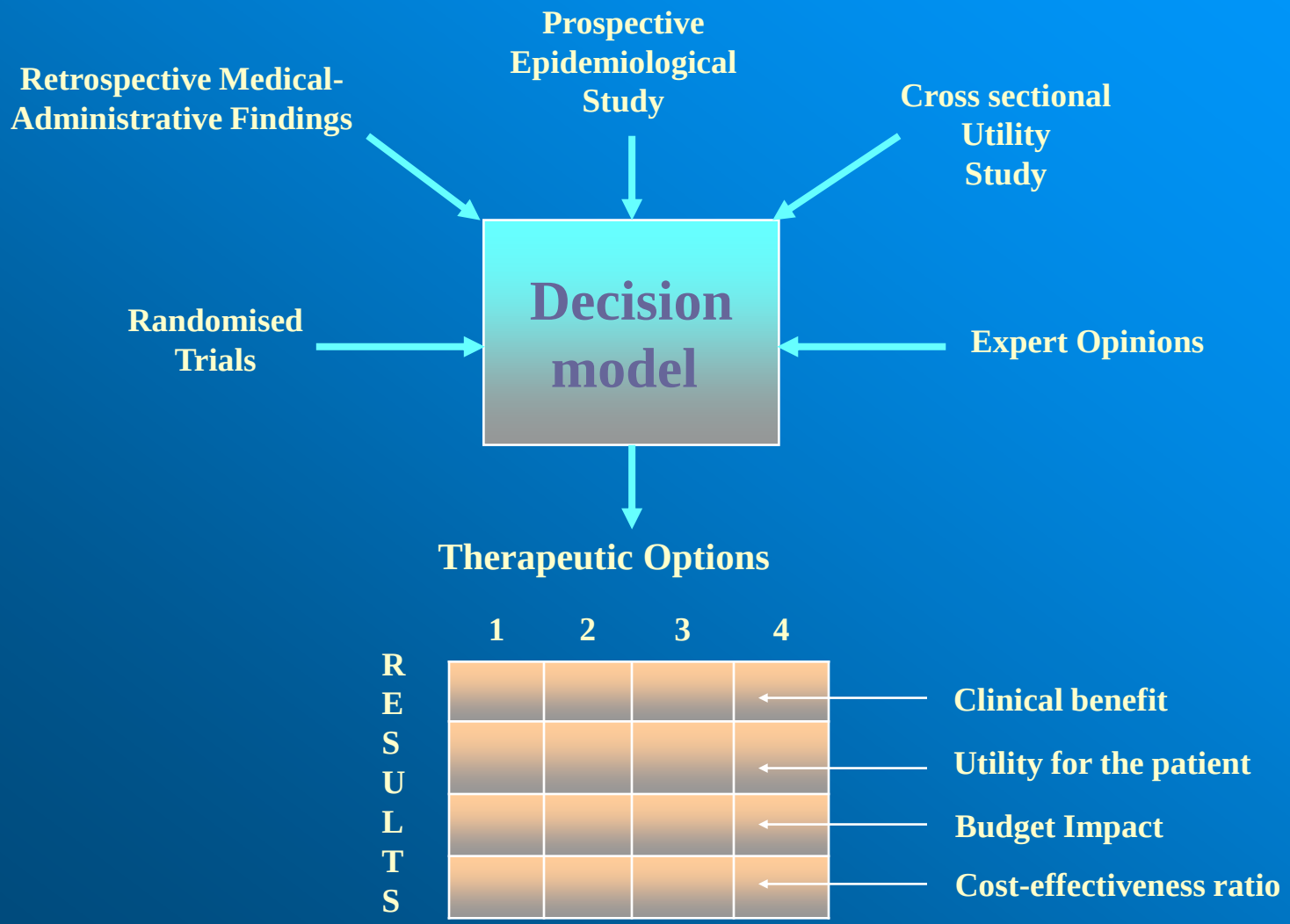
Modelisation:

REES France, Faculty of Medicine - Université Paris XIII - France

launois.rees@wanadoo.fr

http://www.rees-france.com

A Systematic Approach to Identify Treatment's Outcomes Using Data From Different Sources



Why, and When ?

- **No direct comparison between the Products**
  - ⇨Indirect Comparison needed
- **Heterogenous data sources**
  - ⇨ Clinical, psychological, economical
- **Limited time horizon**
  - ⇨ Follow up of the patient from the beginning of the treatement till death

A Case Study In Severe Sepsis

- Severe sepsis: approximately 54,000 cases per year, mortality rate at least 28.5% *(PMSI 99)*
- Cost of care in intensive care units and clinical departments: 26 449.90 € $_{96}$ *(CUB Réa)*
- A new treatment allows the absolute mortality rate in this indication to be reduced by 6.1%: recombinant human activated Protein C (Xigris®) *(Bernard G, NEJM 2001)*

Treatment Strategies

- Conventional treatment (Usual Care)
  - In intensive care unit
  - Procedures described by the Oméga field
- Xigris®
  - Continuous infusion for 96 hours
  - 24 µg/kg/h
  - In addition to normal intensive care practices

Analytical Context

- **Population:** All patients with severe sepsis (and with least one organ system failure, originating from an inflammatory problem with a documented infectious focus)
- **Strategies compared:** Usual Care and Xigris®
- **Perspective:** Public hospital administration
- **End points:** Survival (years of life) and Cost
- **Temporel Horizon:** From the start of treatment in intensive care to death (including outside hospital)

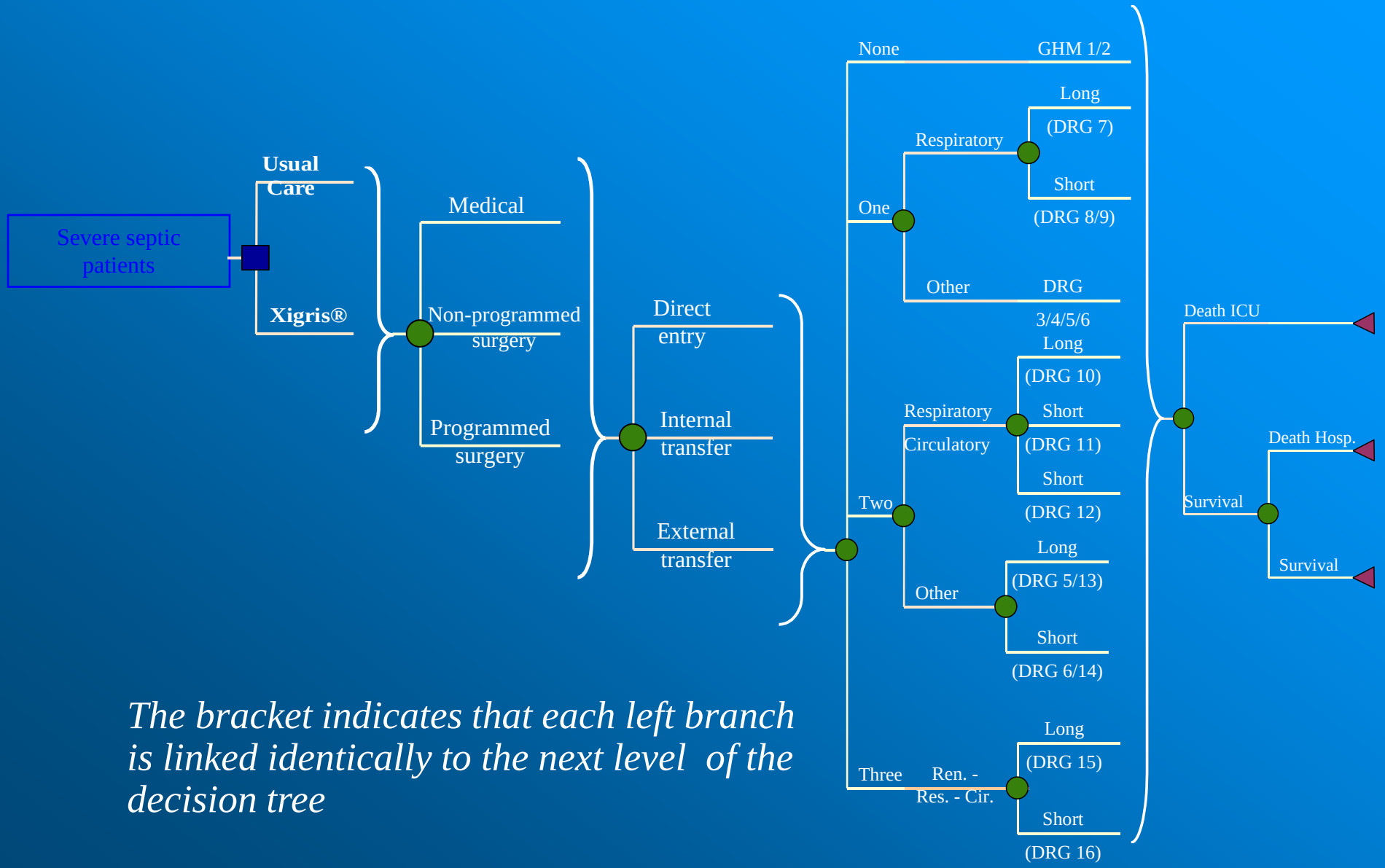
Choice of a Classical Decision Tree

- **Transparency**:
  - Simple understandable tree
  - Directly legible parameter values
- **Exhaustivity**: Integration of various sources of data
  - CUB Réa
  - PROWESS
  - Literature
- **Adaptability**: Ability to introduce new data

List of Variables

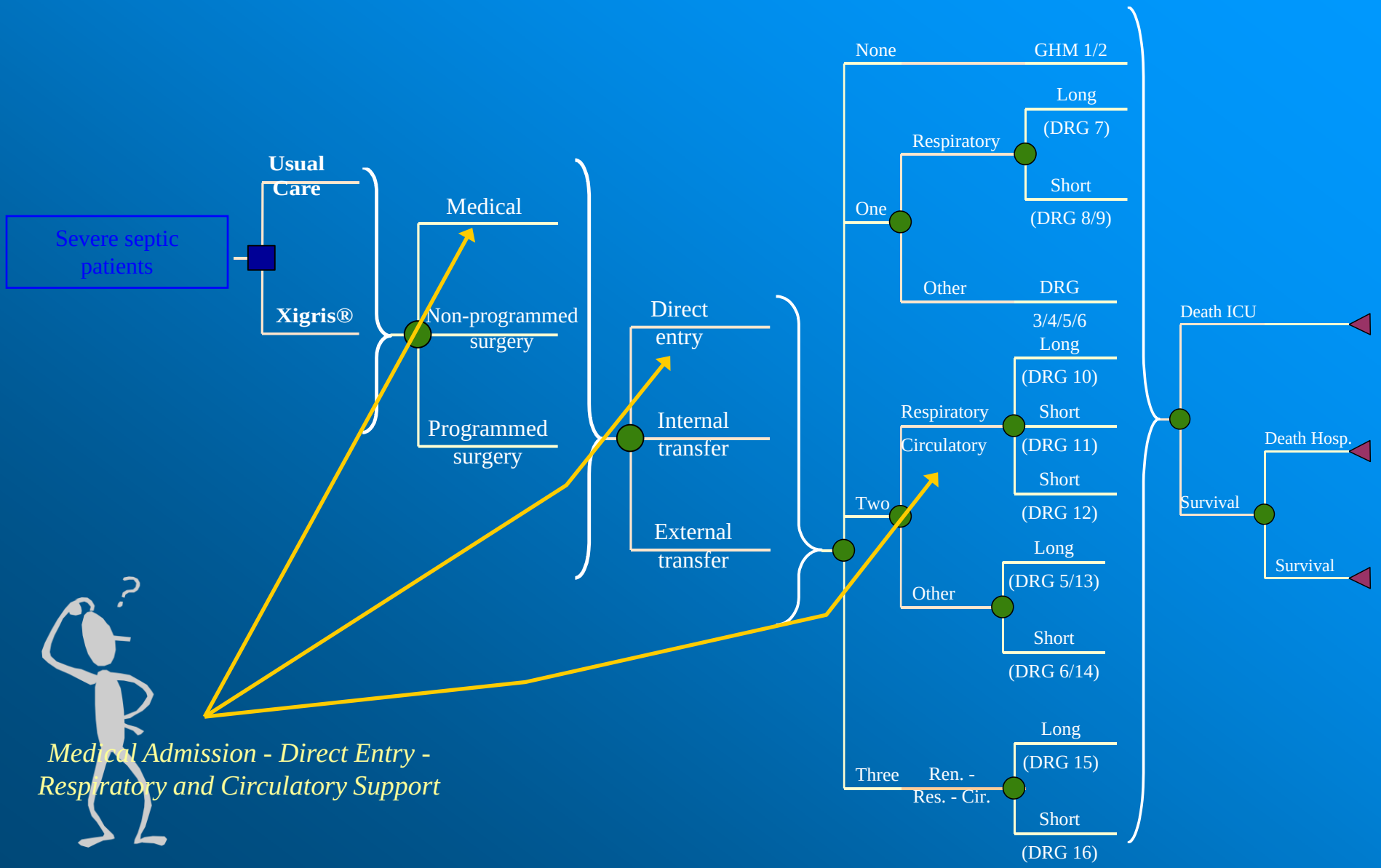
- Admission category: surgical, medical
- Method of admission: direct, transfer
- Number of supports: None, 1, 2, 3
- Type of support: renal, respiratory, circulatory
- Duration of support (Ω score)
- Risk to life (IGS2 score)

Reduced Form of Model

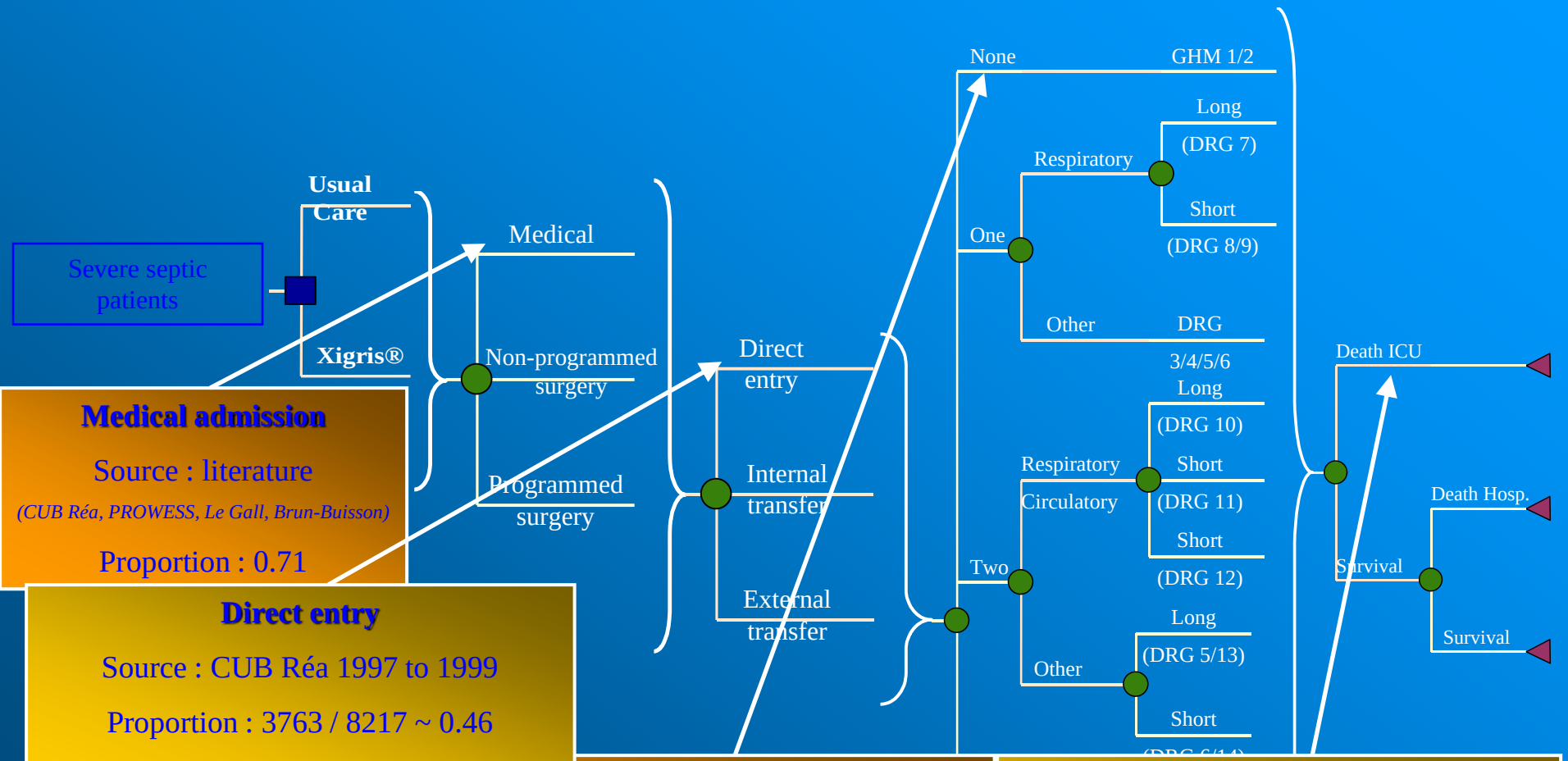


The bracket indicates that each left branch is linked identically to the next level of the decision tree

Patient Trajectory



Allocation of Probabilities



Medical admission

Source : literature

(CUB Réa, PROWESS, Le Gall, Brun-Buisson)

Proportion : 0.71

Direct entry

Source : CUB Réa 1997 to 1999

Proportion : 3763 / 8217 ~ 0.46

Cumulative Proportion : 0.71*0.46 ~ 0.33

No organ support

Source : CUB Réa (97 to 99)

Proportion : 620 / 3763 ~ 0.16

Cumulative Proportion : 0.33*0.16 ~ 0.05

Death in Intensive Care

Source : CUB Réa (97 to 99)

Proportion : 12/620 ~ 0,02

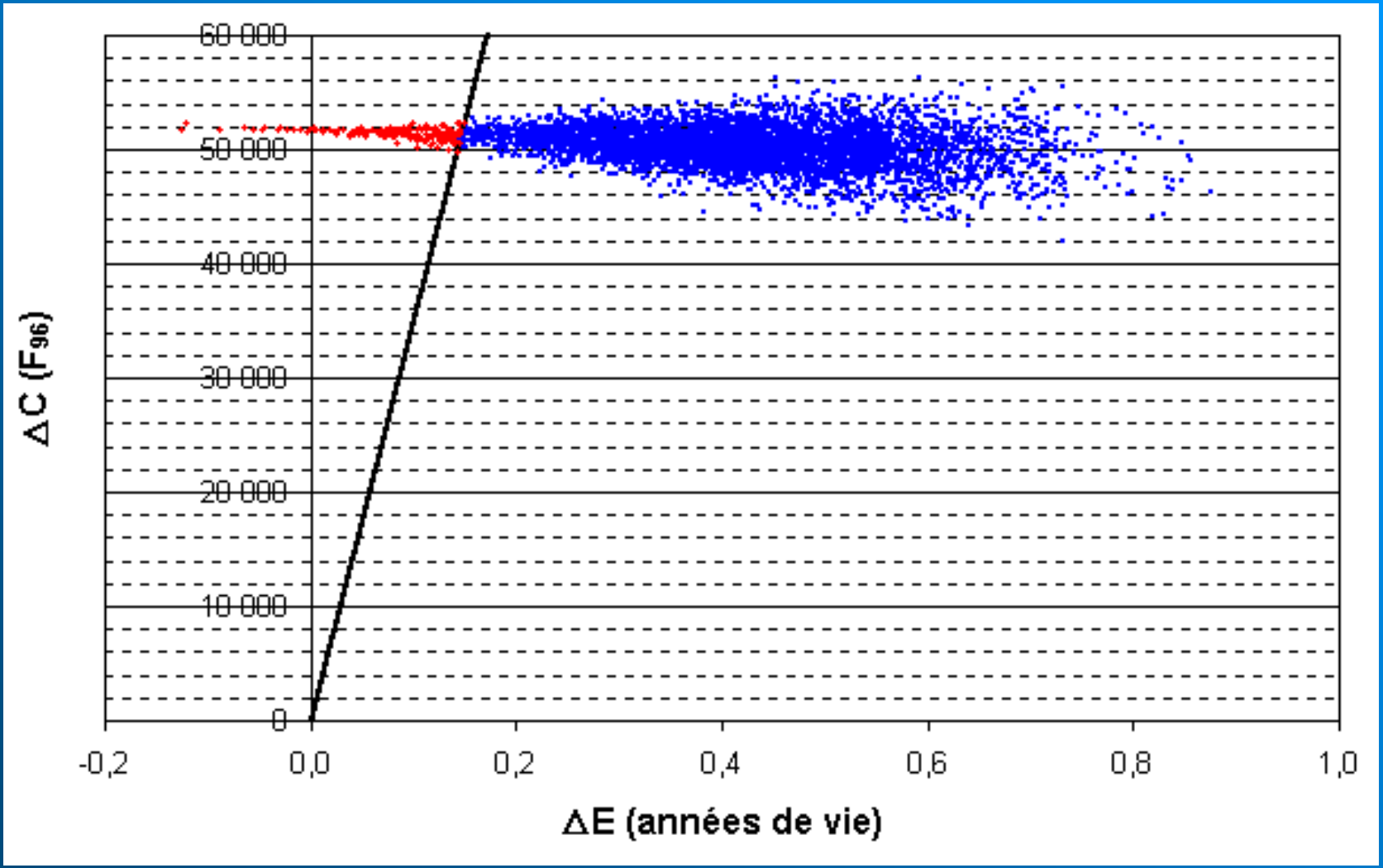
Cumulative Proportion : 0.02*0.05 ~ 0.001

Incremental Cost-Effectiveness Ratio All Situations Combined

Strategy	C (Euros €96)	ΔC	E (years)	ΔE	ΔC/ΔE
Usual Care	26 907.40		4.6042		
Xigris	34 586.41	7 679.10	5.0200	0.4158	18 467.98

Probabalist Sensitivity Analysis

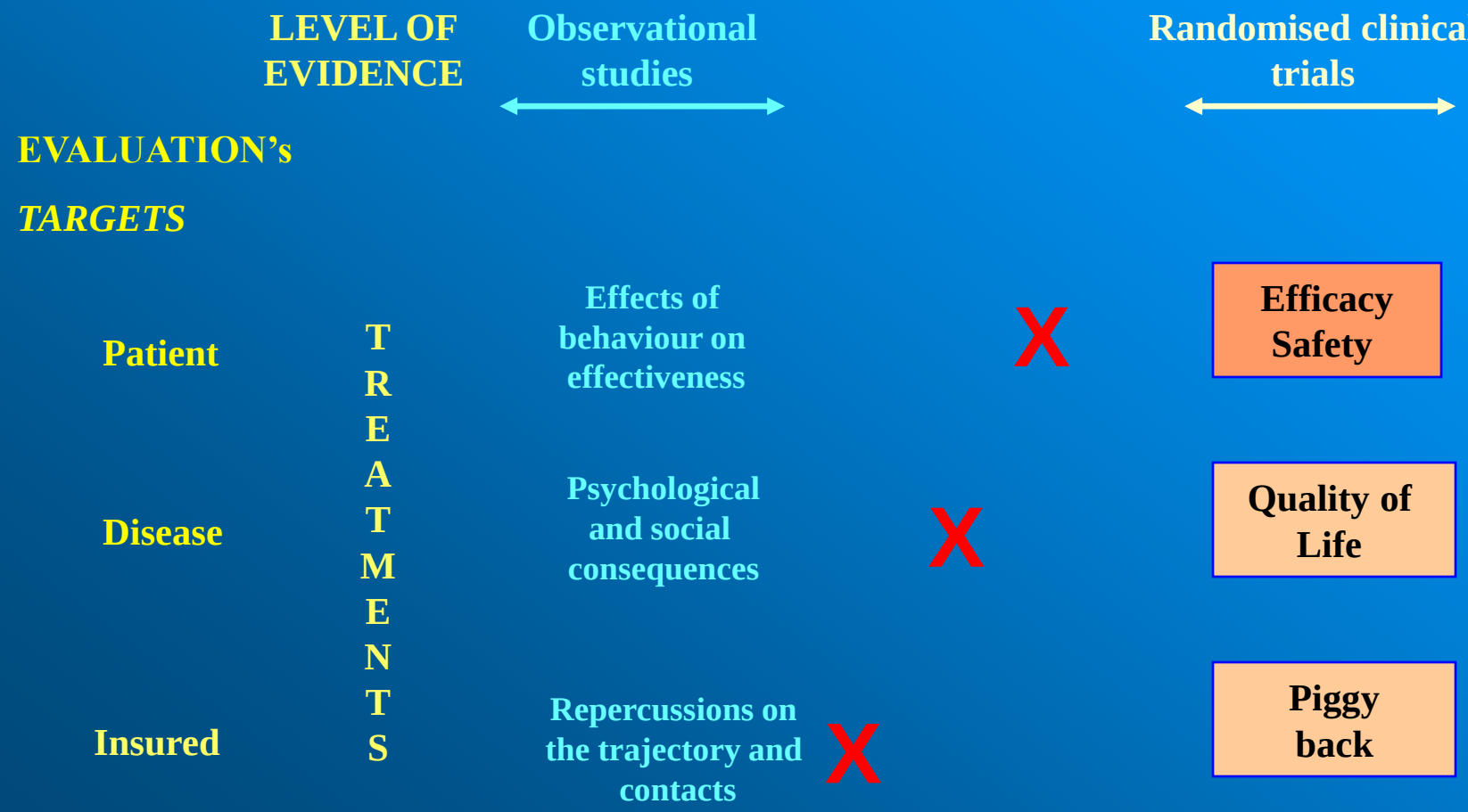
Cost-Effectiveness Quadrant



Conclusion

- Treatment with Xigris® is no more expensive than some interventions affecting patients of the same age
- The value of this ratio is improved considerably by targeting patients with at least two organ system supports
- Cost of care is not the most sensitive variable in defining the ratio

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



Second Attempt:The Search for Effectiveness

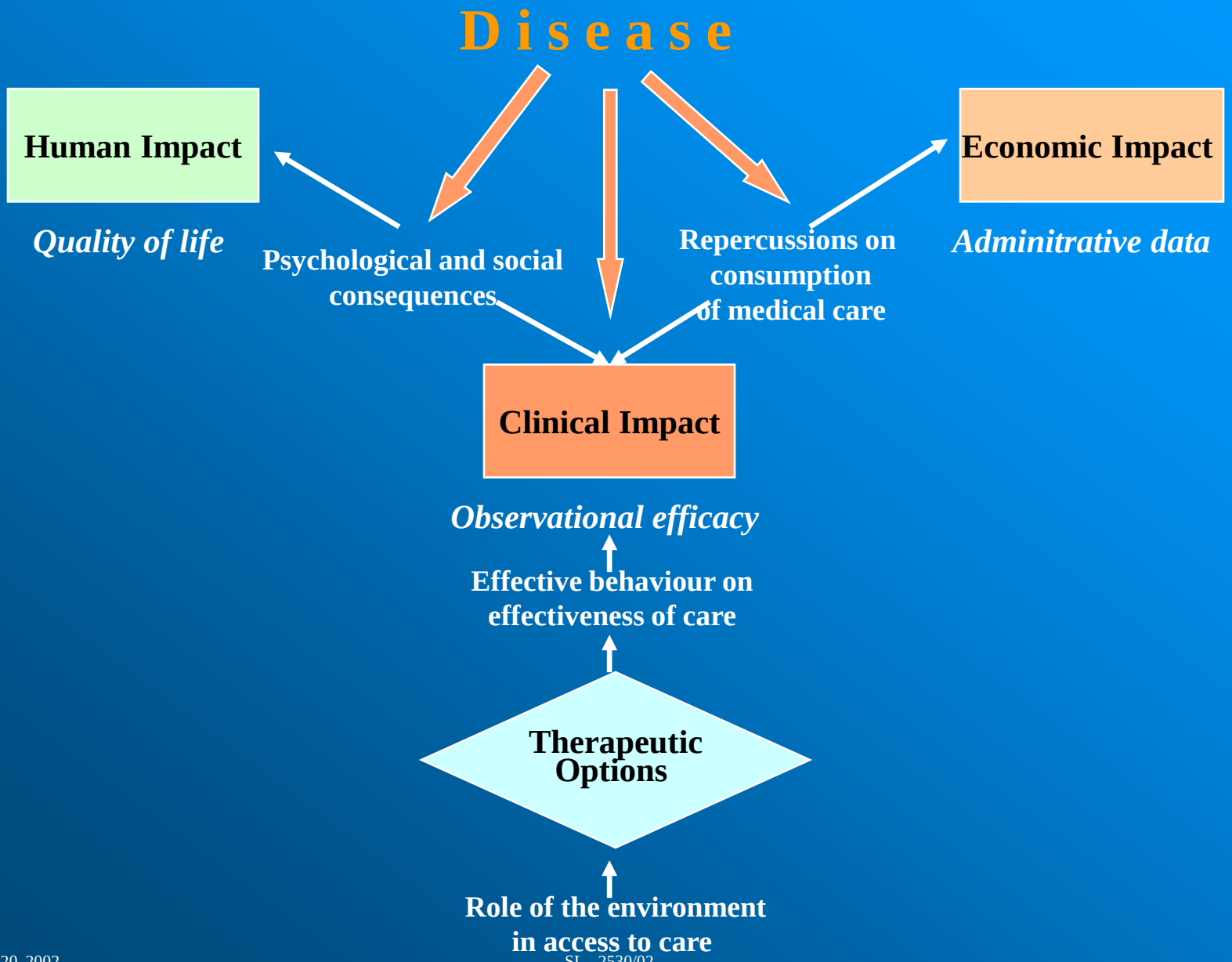
The Practice of a More Holistic Medicine

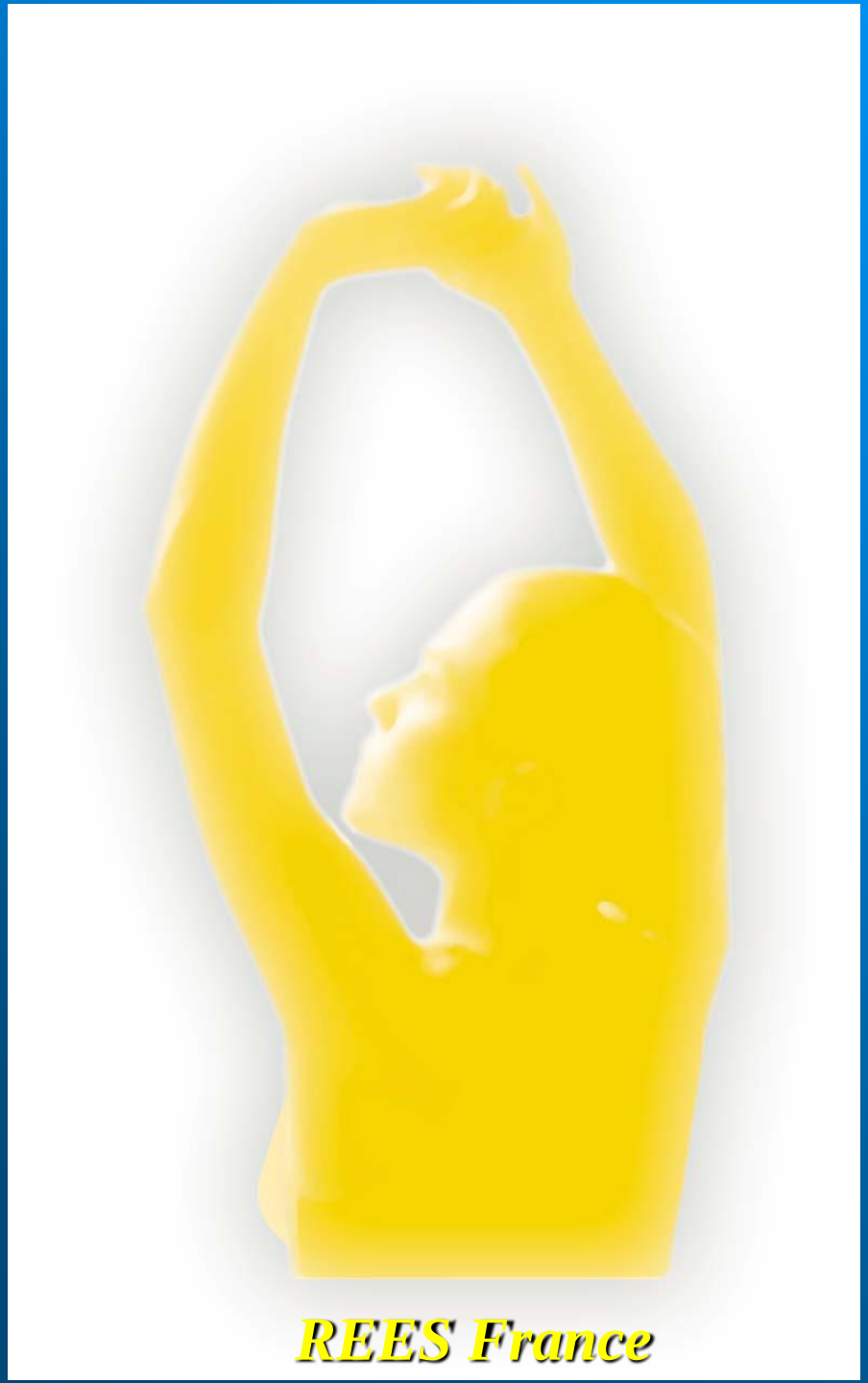
Requires the formation of

Records of **C**linical, **H**uman based, **E**conomic and **S**ocial Information in **H**ealth

in the context of everyday medical practice

Analysis of the «*RICHESS*» Creation





REES France

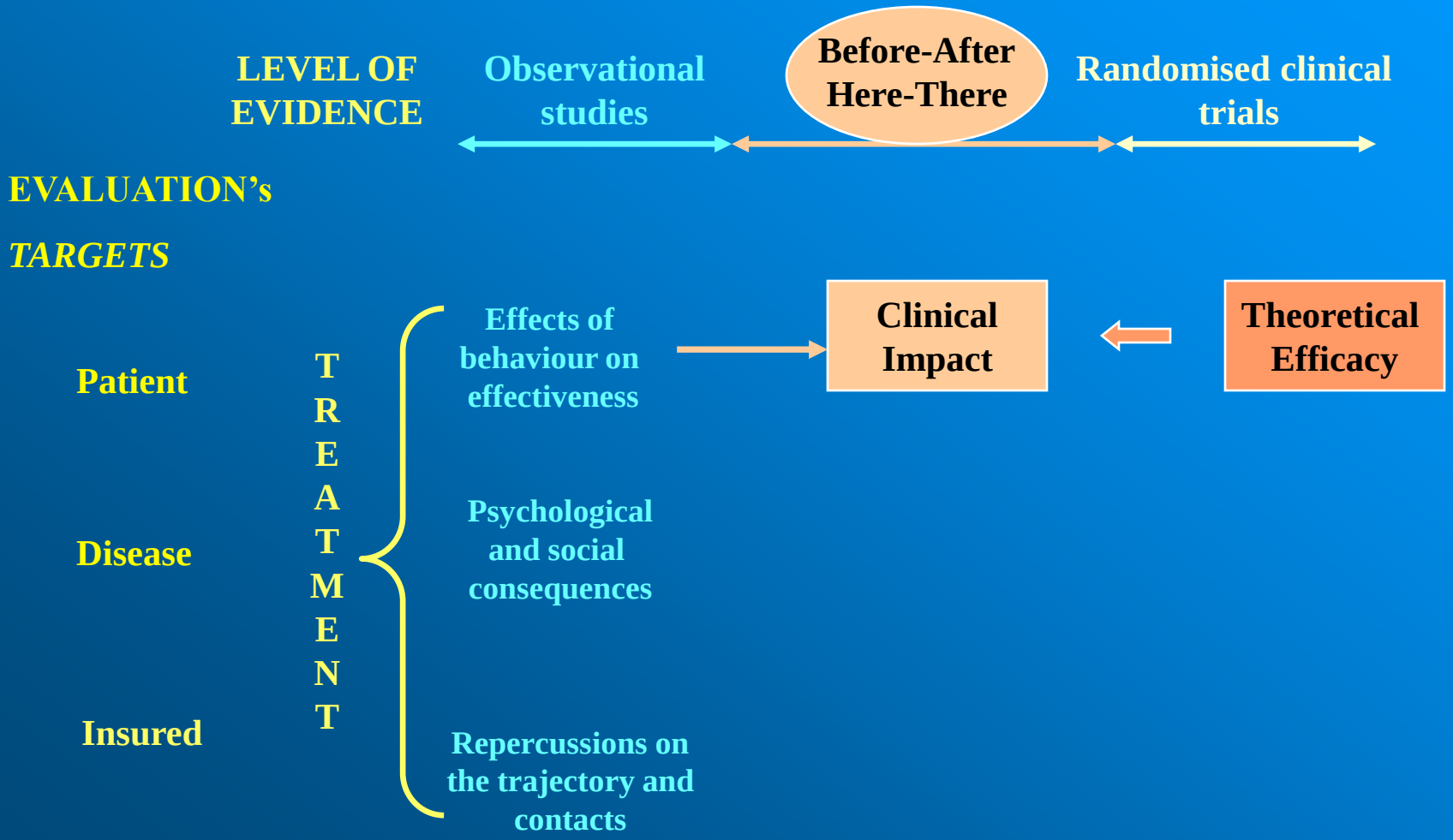
Post Market Approval Studies:

REES France, Faculty of Medicine - Université Paris XIII - France

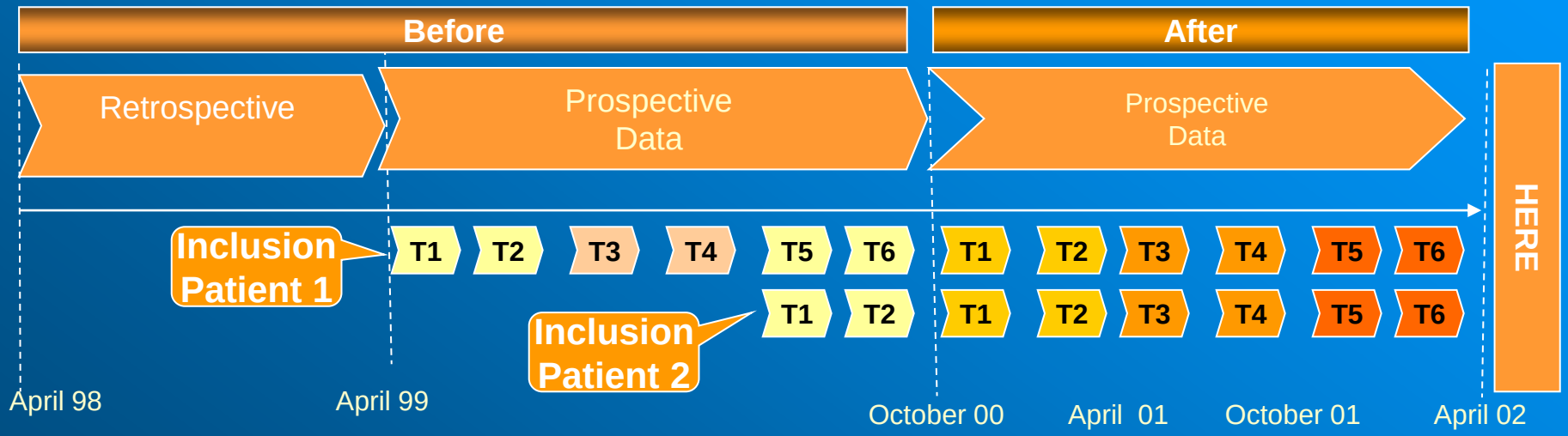
launois.rees@wanadoo.fr

http://www.rees-france.com

Choose a Quasi-Experimental Study Plan

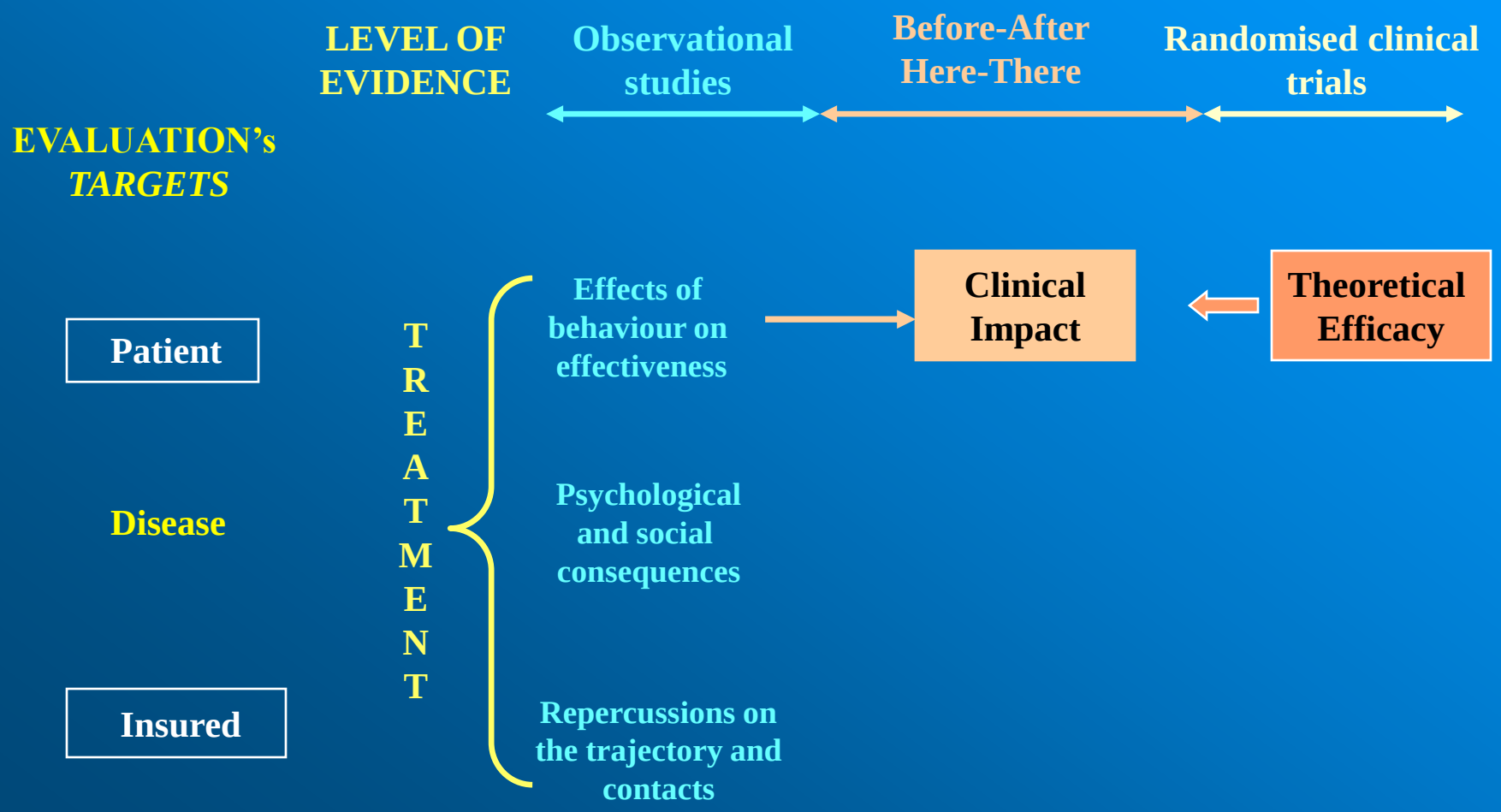


Study Design
«Before-After» Comparison



T=Quarter after inclusion

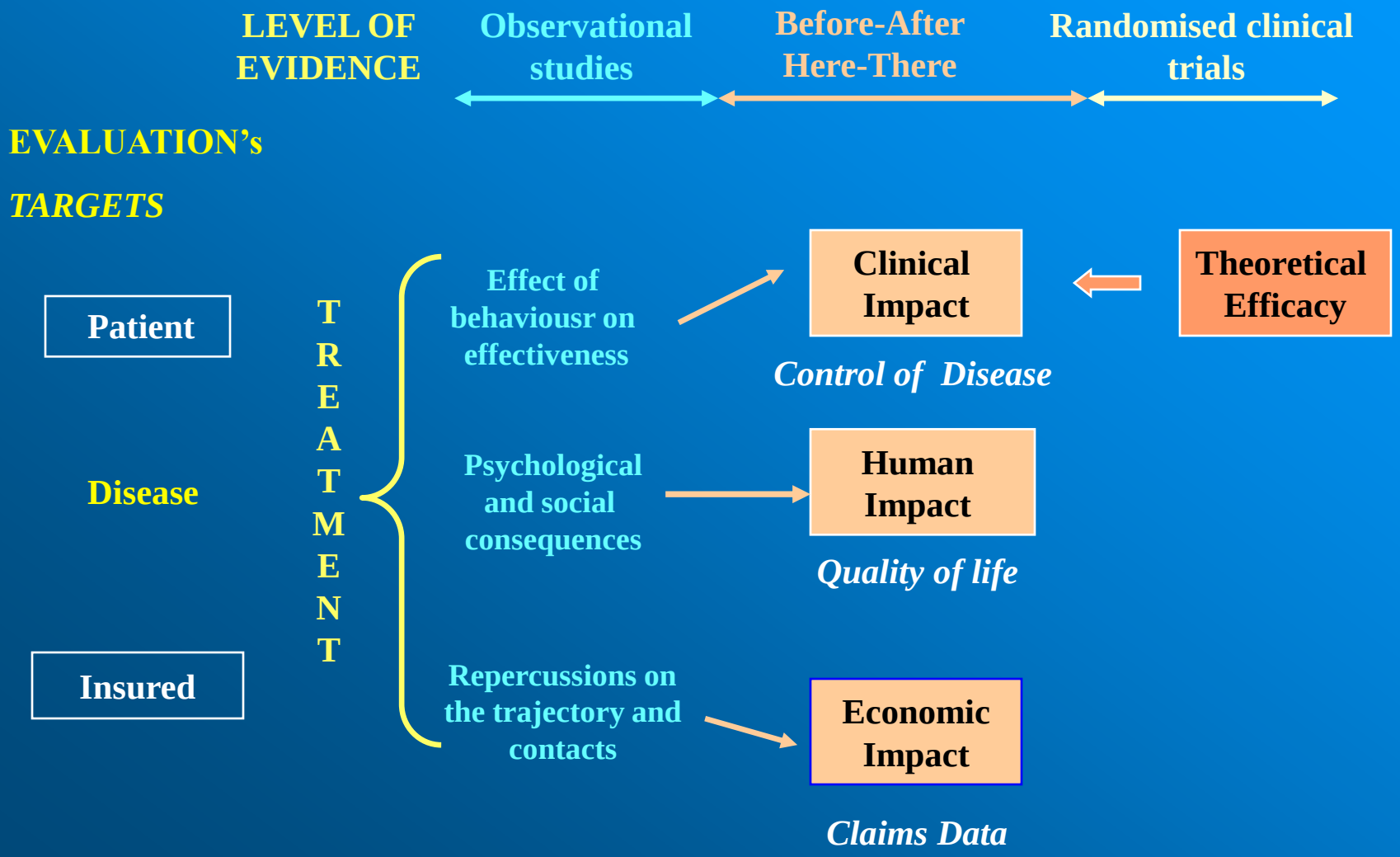
Prioritise the Patient and the Contributor Rather Than the Disease



With New Evaluation Criteria

- ***Clinical Impact: observational efficacy***
  - Variability of practices
  - Quality of compliance
  - Control and non-control of the disease
  - Effects of education and training
- ***Human Impact: benefits obtained in life***
  - Reduction in symptoms
  - Reduction of functional disability
  - Improvement in quality of life and satisfaction
- ***Economic Impact: changes in cost***

Select Operational Indicators



Control and Non-Control of Symptoms for Clinical Impact

A Case Study In Asthma

Composite criteria based on the criteria of the Canadian consensus*:

- **Day-time symptoms**
- **Night-time symptoms**
- **Exacerbations of the asthma**
- **Loss of work and absence from school**
- **Consumption of Beta2 mimetic agents CA**
- **Peak Expiratory Flow Rate**

* Boulet et al.:CMAJ 1999.10: S1-S9

Thresholds for Non-Control

Criteria	Canadian Consensus
Day-time symptoms	> 6d /7 d
Night-time symptoms	> 1 night/week
Exacerbations	1 since the last consultation or causing the consultation on the day
B_2SA	> 6d /7 d
FEV1	< 80 %
Loss of work	Yes

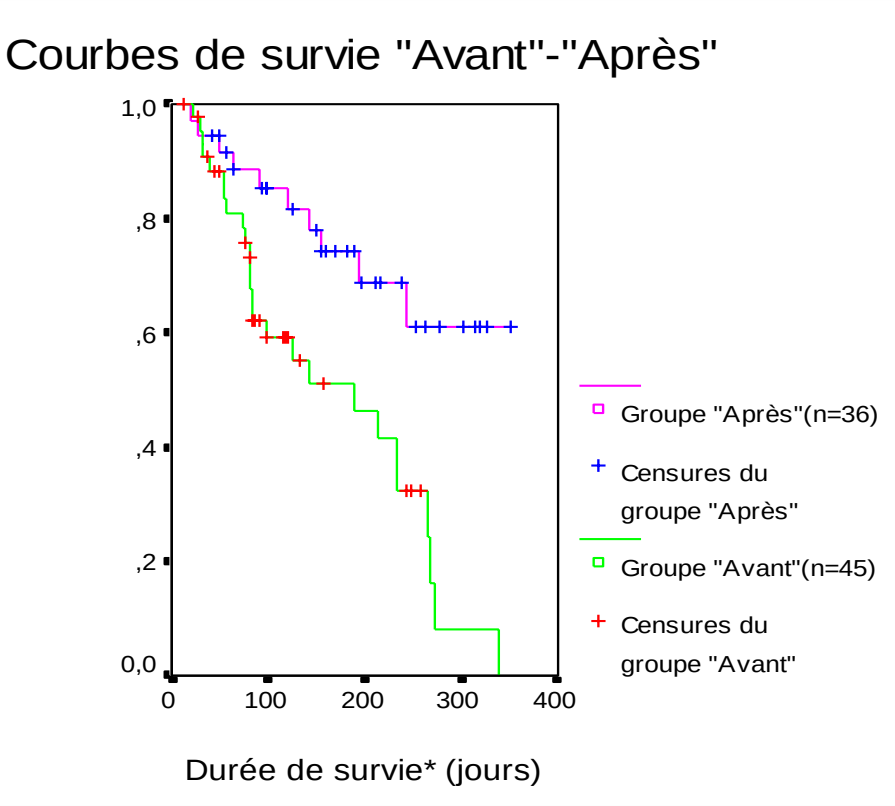
Quarterly Evaluation of Control:

- State of control/non control was assessed for each of the consultations
- The number of consultations with control and without control was counted by quarter
- If the number of non controlled consultations was > than the number of controlled consultations during a quarter ⇒ patient is not controlled for the trimester

Treatment of Missing Data

- If one or more of the 6 criteria characterising control is not documented,
- Without one of the thresholds being breached when the other items are completed,
- Then, the patient is assumed to be controlled.

Comparison of Time Spent with Controlled Asthma Before and After Intervention



Estimation of median time before becoming non controlled:

Before : 190 days
CI (95%) = [84 , 266]

After : > 352 days
CI (95%) = [243 , .]

P = 0.002

** Survival time (days) = time between first follow up consultation (controlled) and becoming non controlled*

Quality of Life Scales for Human Impact

Human Impact: Benefits Obtained in Life

Health Related Quality of Life: A Buzz Word ?

- ***The field is limited to the repercussions of the disease and its treatment.The concept has two fundamental components :***
- ***Subjectivity: quality of life supposes an ability to describe the hardship experienced. Only the patient can perform this task.***
- ***Multidimensionality: life cannot be evaluated in general; its various dimensions have to be investigated.***

Categories of Scales

- **Generic scales** are trans-symptomatic instruments which apply to all diseases. The best known are the Sickness Impact Profile (SIP), the Nottingham Health Profile (NHP) and the SF-36 .

- **Specific scales** focus on fields which have a major impact on the repercussions of the disease in order to increase the sensitivity of the indicator, i.e. the ability to detect low amplitude differences but differences which may be clinically significant.

How is the Scale Constructed?

- *Phase 1* : Qualitative survey
  - Collection of verbatim reports
  - Formation of a question bank
- *Phase 2* : Quantitative survey
  - Reduction of the questionnaire
  - Identification of dimensions
- *Phase 3* : Validation survey

Qualitative Survey

- Construction of an interview guide by theme
- Collection of verbatim reports: semi-structured interviews
- Classification of verbatim reports by dimension
- Choice of a method of questioning
- Drawing up wording
- Standardising the Items

Questionnaire V00

Quantitative Survey

- Reduction of the questionnaire: Removal of variables
  - Not documented
  - Non discriminatory: ceiling effect, floor effect
  - Redundant: e.g. correlation > 0.7
- Identification of ACP dimensions

Validation Survey

Three conditions

- ***Reliability*** **:** ***Do the answers to the same questions remain the same at two different periods of time on stable patient ?***

- ***Construct validity*****:** ***Do the correlations between the quality of life scores, internal subscores and external criteria such as clinical end points or other quality of life scale fit the expected relationships?***
  - Structural validity :*Internal consistency of dimensions Discriminatory potential of questions*
  - Clinical validity : *correlations with the clinical data*
  - Convergent validity: *correlations with other quality of life scales' dimensions*

- ***Responsiveness*****:** ***Do we observed changes in scores in patients whose states of health is deteriorating or improving ?***

Psychometric Norms

Caractéristics	Statistical Tests	Validity thresholds
Reliability	Intraclass correlation coefficients (ICC) across stable patients at D0-D28 Cronbach ∝ coefficients	> 0,80 > 0,70
Construct validity : *Structural validity*	Item scale corrélation coefficients at D0	> 0,40
Construct validity *Clinical validity*	Spearman correlation coefficients at D0 with clinical end points	P < 0,05
Construct validity *Convergence validity*	Spearman correlation coefficients at D0 with homologous dimensions of validated quality of life scales	
Responsiveness	Effect size	> 0,40

A Case Study In Upper Limb Lymphœdema

- The existing classifications for upper limb lymphœdema (ULL), based on œdema volume, underestimate disturbance
- Specific concepts of upper limb lymphœdema are not assessed by generic quality of life scales: NHP ,SIP,SF-36

Aims of the Project

- To construct a specific evaluative quality of life scale in upper limb lymphedema secondary to breast cancer
- To evaluate changes in patients ' quality of life on treatment in this situation

Development Stages of the Quality of Life Scale ULL-27

- ***Phase I*** **: qualitative survey (24 patients)**
  - collecting verbatims reports : 1 166
  - formation of the bank of 70 questions
- ***Phase II*** **: quantitative survey (154 patients)**
  - reduction to produce the initial questionnaire : 28 items
  - identification of the dimensions
- ***Phase III*** **: validation study (304 patients)**

Items Generation

Qualitative Survey : n=24

- Interview guide based on information collected from literature and experts
- 24 semi-structured interviews
- 3 groups of patients
  - unaffected patients afraid becoming worse
  - patients physically / psychologically affected
  - patients with progressing problems
- 1 124 items collected

Wording of the Question

Verbatim report

« I think everyone is looking at me, that is the end »

«The assistant in the dressing-room is staring at me, it's awful »

Question

Q51 : Do you think that other people are staring at you ?

Item Reduction

First Quantitative Survey : n = 154

V00 administered to 154 patients

- Missing variables
- Non discriminatory variables
- Redundant variables ($R^2 > 0.70$)
- Independant variables ($R^2 < 0.40$)
- Variables with loading factors < 0.50

Validation Study

Second Quantitative Survey : n = 303

- Reliability
- Construct Validity
- Responsiveness

Concurrent Criteria

- **Difference in volume between the healthy limb and the affected limb:** ***addition of cone trunks***
- **MD's Global Clinical Impression (GCI) :** ***1 dimension, transitional scale : (+),(=),(-)***
- **Patient's Arm Comfort Scale (VAS) :** ***1 dimension, transitional scale : (+),(=),(-)***
- **Global Symptom Index (GSI) :** ***heaviness, tension, hardness - addition of the 3 products freq * severity ; 1 dimension and a global score***
- **Generic quality of life scale :**

  SF36 ***(8 dimensions)*** **PF-RP-BP-GH-VT-SF-RE-MH**

Reliability

- Reproducibility in stable patients (D0/D28)
  - Physical dimension : 0.86 ($p<0.001$)
  - Psychol. dimension : 0.80 ($p<0.001$)
  - Social dimension : 0.70 ($p<0.001$)
- Cronbach alpha coefficient
  - Physical dimension : 0.93
  - Psychol. dimension : 0.86
  - Social dimension : 0.82

Structural Validity :

Multi-traits/Multi-items Matrix

	PHYSICAL DIMENSION (15 ITEMS)	**PSYCH. DIMENSION** (7 items)	**SOCIAL DIMENSION** (5 items)
Internal consistancy of items	0,48 - 0,71	0,42 - 0,77	0,55 - 0,71
Success rate ($r \geq 0.40$)	100%	100%	100%
Discriminatory ability of items	0,23 - 0,48	0,13 - 0,60	0,27 - 0,52
Success rate ($r1 \geq r2$)	93%	100%	100%

⇨ ***Good internal consistency but a moderate discriminant validity***

Clinical Validity :

Comparison of the ULL27 Dimensionnal Scores at D0 Accross Severity Stages

	PHYSICAL	PSYCHOL.	SOCIAL
Stage1-n=30	65,27	62,05	71,50
Stage2-n=47	57,17	61,72	63,80
Stage3-n=69	51,74	61,64	63,53
Stage4-n=90	50,54	61,62	55,99
P (ANOVA)	0,008	0,99	0,02

* *n minimum*

⇨***Good correlations between quality of life scores and clinical stages verify the clinical validity of the instrument***

Convergent Validity:

Correlations between the ULL-27 Subscales and the other Scales at D0

Are statistically significant and > 0.50 between

- **Physical Dimension :**

  SF36 subscales : PF (0,515) BP (0,649) VT (0,555)

  GSI *(Global Symptoms Index)* (0.557) - VAS *(Arm Comfort Scale) (0.531)*
- **Psychological Dimension :**

  SF36 : VT (0,529) MH (0,732)
- **Social Dimension :**

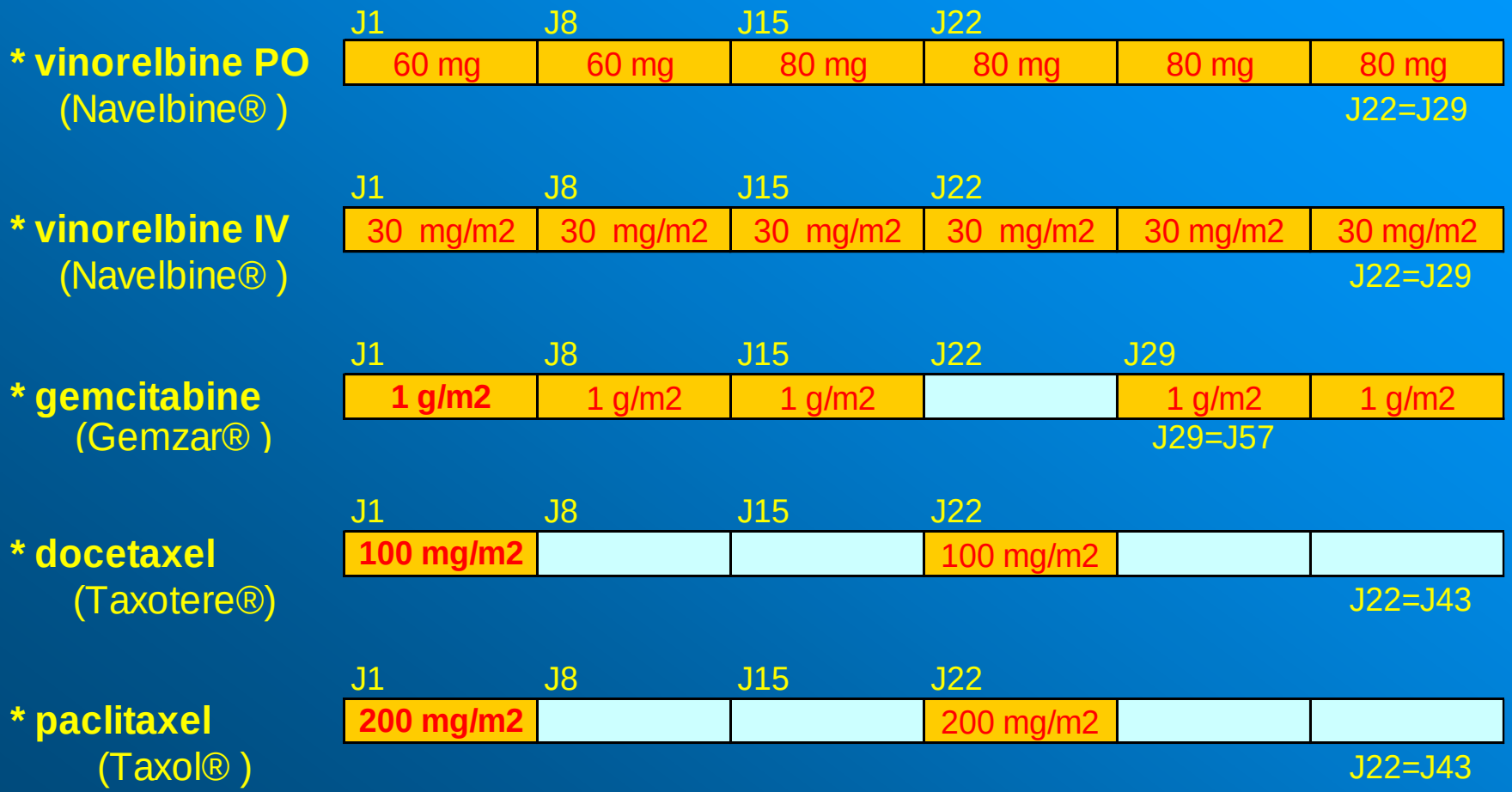
  SF (0,579) - MH (0,528)

Administrative and/or Medical Data Bases For Resource Utilization Information

A Case Study In Lung Cancer

- Lung Cancer is a **second leading** cause of death due to cancer throughout the world : a public health problem
- In Small Cell Lung Cancer is **the commonest** form of lung cancer, making up 80 % of cases
- **25 %** of patient present with an **operable tumor**. Most of the patient are treated by chimotherapy

5 First line Mono-Chemotherapy Options in NSCLC Cancer



Hospitalisation Cost ($€_{99}$)

DRG (Scale PMSI 1999)	ISA coefficient	Full cost
Cost treatment		
Chemotherapy course with full hospital admission (DRG **587)**	839	1 587.60
Outpatient chemotherapy course (DRG **681**)	204	386.46
Cost of toxicities		
Sepsis – Febrile neutropaenia (DRG 604)	2 372	4 489.47
Blood Transfusion (DRG 819)	248	579.46
Nausea – Vomiting (DRG 122)	1 274	3 376.44
Diarrhoea – Constipation (DRG 142)	788	1 491.26

National Value of ISA point : 1.89 €

Breakdown of the DRG 681 « Outpatient Chemotherapy » Costs

	Standard Treatment Cost (€$_{99}$)
Variable medical costs:	
Medicine products – Medical consumables	96.0
Laboratory	26.37
Radiology	7.17
Dialysis	1.68
Radiotherapy	0.9
Others	102.29
Total	234.62
Fixed medical costs	99.55
Variable infrastructure costs	12.65
Fixed infrastructure costs	39.64
Outpatient chemotherapy session : DRG 681	386.46

Actual Drug Costs of IV Chemotherapies In NSCLC

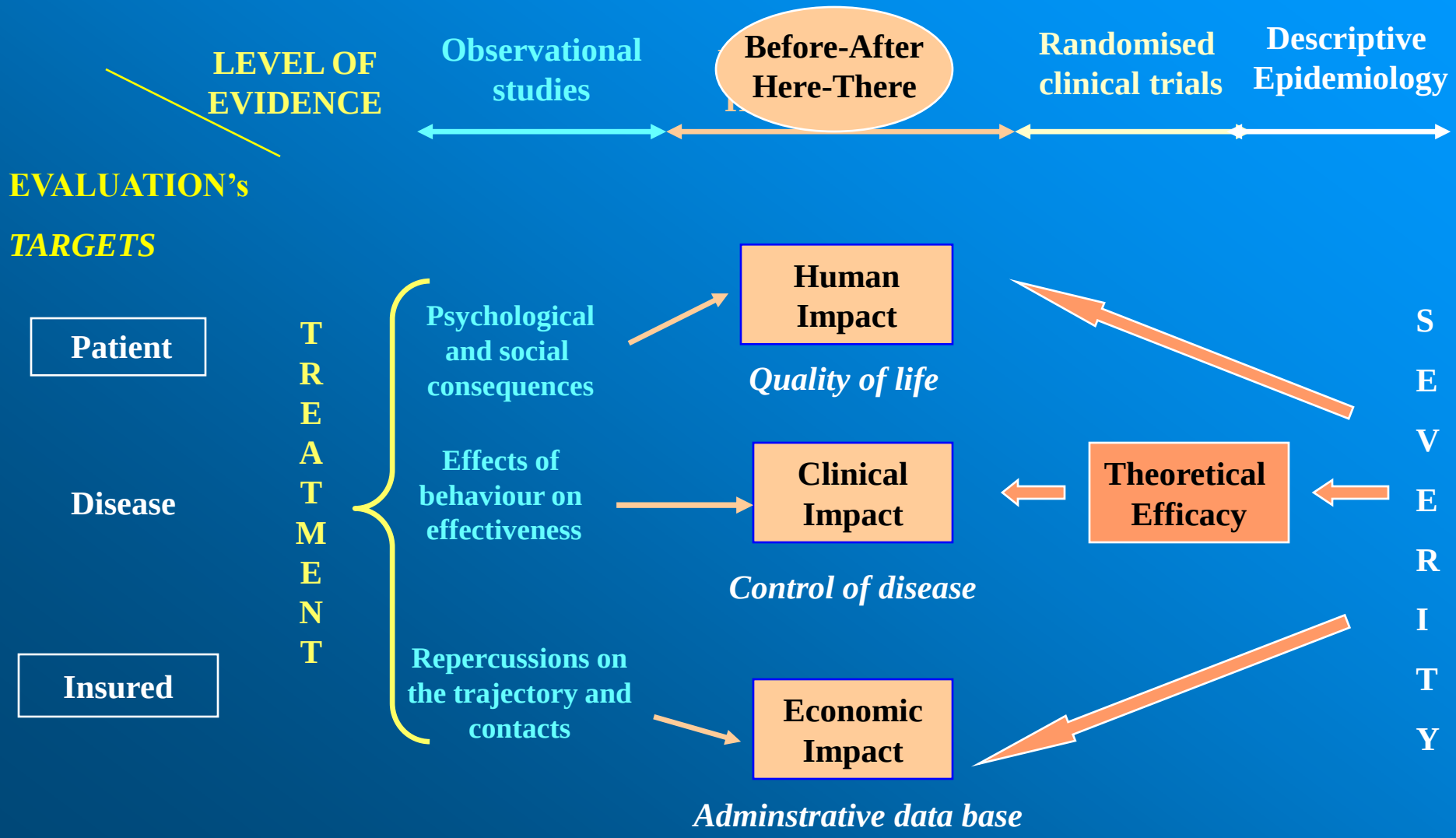
Standard body surface area: 1.7 m^2

	Conditioning	Duration of course (weeks)	Cost of course (€ 99)	Cost per week (€ 99)	
Vinorelbine IV	10-50 mg	1	135,98	136,00	($ 117)
Gemcitabine	200-1000 mg	4	905,90	226,23	($ 213)
Vinorelbine PO	20-30 mg	1	329,29	329,29	($ 280)
Docetaxel	20-80 mg	3	1465,49	448,45	($ 385)
Paclitaxel	30-100 mg	3	1740,51	580,22	($ 500)

Actual IV Hospital Treatments Weekly Cost In NSCLC (€99)

Per week	vinorelbine	gemcitabine	docetaxel	paclitaxel
° Cost of DRG 681 **net of medical consumption**	290	217	96 ,8	96;8
° Medical consumption specific to the cytotoxic agents				
* Chemotherapy started	136	226	448	580
*Associated treatments	2	2	1	1
* Minor items of equipment *(Vergnenegre 1998)*	29	21	9	9
Total cost of DRG 681, adjusted per week	**457**	**466**	**595**	**687**
° Transport *(Fouquier 1996, Le Brun 1997)*	68	52	23	23
Mean cost of a course in hospital, per week	**525**	**518**	**618**	**710**

Operational Indicators Business Summary :



«*RICHESS*» Creation Analysis Versus Clinical Research

	« RICHESS » CREATION	CLINICAL RESEARCH
Perspective	**Patient centred**	**Disease centred**
Object	**Global management**	**Medicinal products**
Method	**Quasi-Experimental method**	**Experimental method**
Theoretical Support	**Social Sciences**	**Basic sciences**
Evaluation criteria	**Effectiveness in common practice**	**Efficacy in ideal conditions**
Analyses	**Consequences of the disease**	**Mechanisms of the disease**

CONCLUSION (1)

THE DEVELOPMENT OF DATABASES INTO WHICH DATA ARE FED BY PROFESSIONALS UPSETS EVALUATION METHODS

- New *end points* developed: changes in *quality of life*, financial repercussions of the decision *seen only from the point of view of its initiator*

- Plans for collecting information which collect « *drop* wise » data become realistic

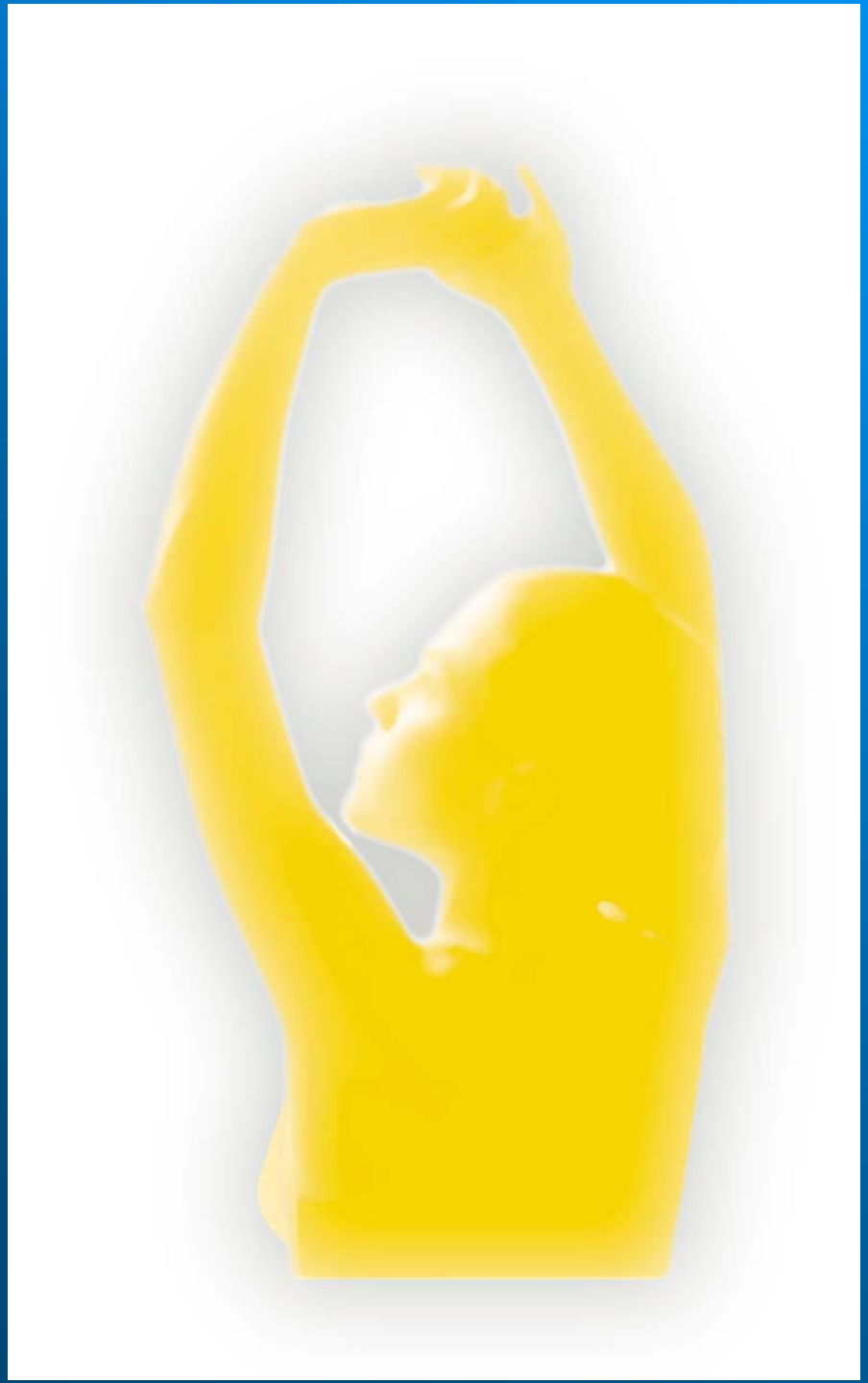
CONCLUSION (2)

Analysis of the « RICHESS » creation

opens a new pathway to evaluation.

In the future it will represent,

a discipline which is independent of clinical research and marketing



Thank You For Your Attention

REES France

Faculty of Medicine - Université Paris XIII - France

http://www.rees-france.com