Early Stage HTA

Valutazione delle Tecnologie Sanitarie

MARTA CAVAGNARO

Quando "si usa"

HTA:

- per scegliere una nuova tecnologia (e.g. in ospedale)
- per verificare se una tecnologia in uso è ancora valida
- durante lo sviluppo di un nuovo prodotto biomedicale
  - Concettuale: nei primi tempi dello sviluppo
  - Sperimentale: quando si è alle prime fasi di test e di valutazioni con l'utilizzo di animali o modelli
  - Investigativo: si sta procedendo con le prime valutazioni cliniche (esseri umani)

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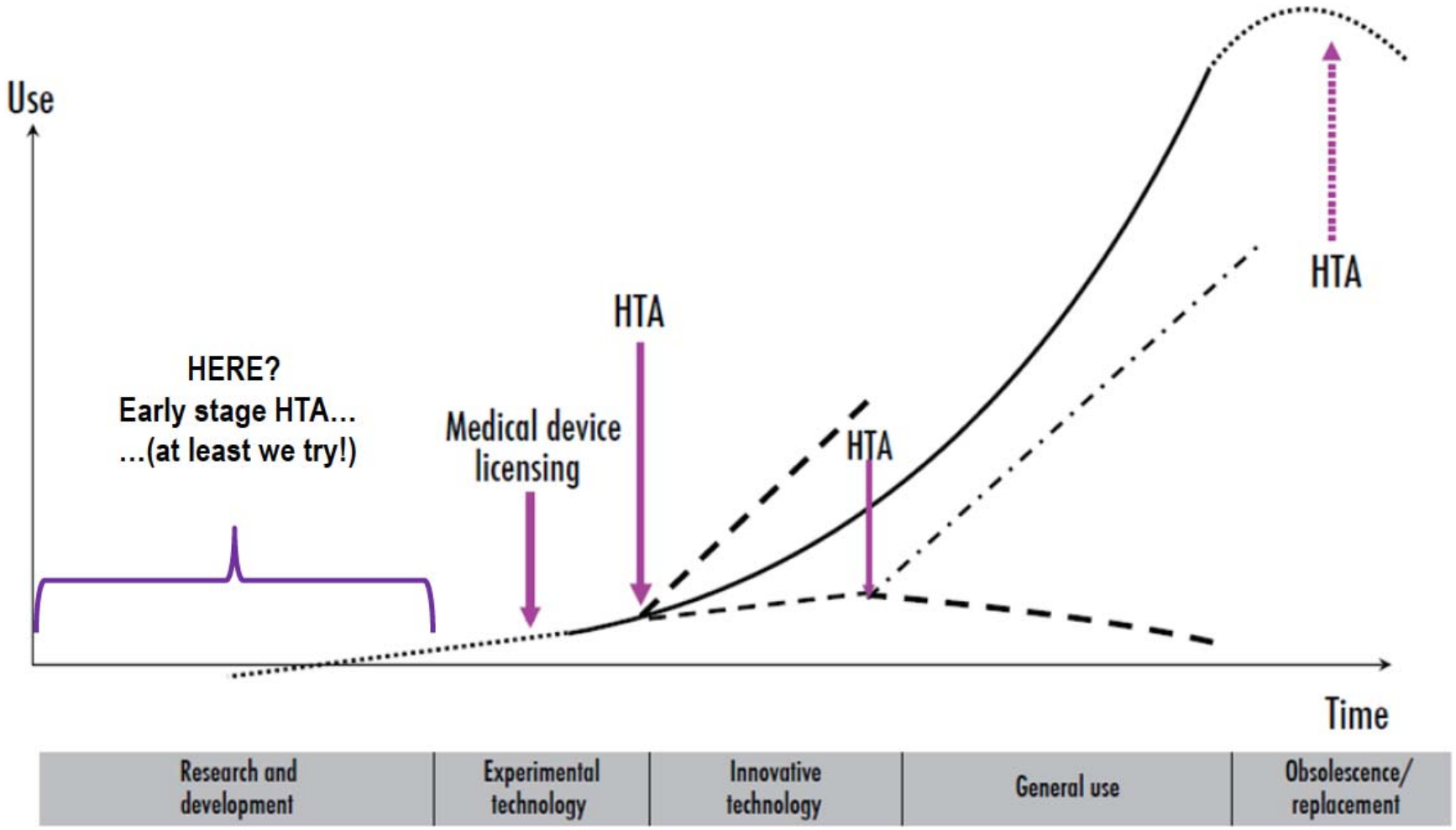
Early Stage HTA

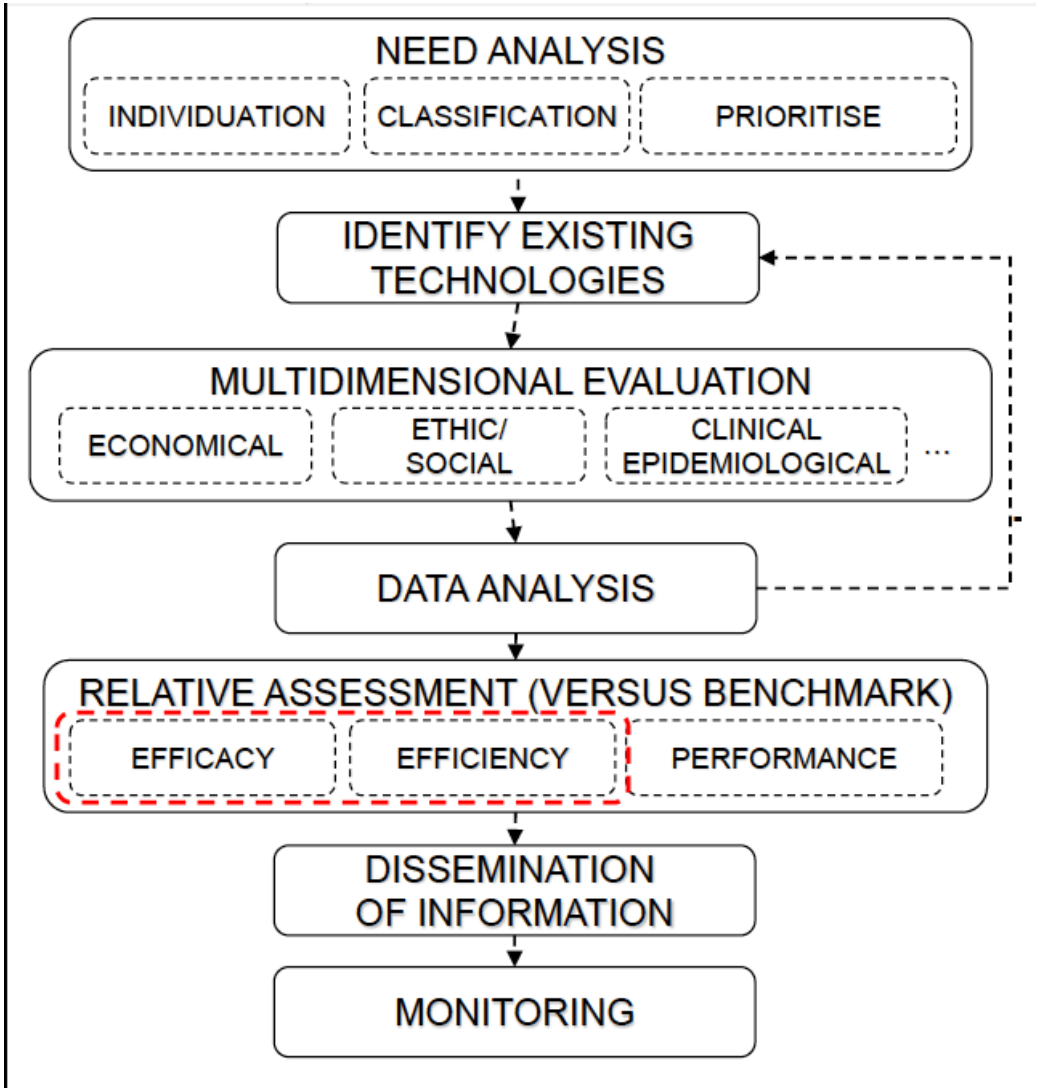
- Se l'HTA viene fatto quando ormai il prodotto è pronto, e non durante il processo di ricerca e sviluppo, il rischio è quello di vedere vanificati mesi / anni di attività…
  - a quel punto viene vista come un ostacolo alla commercializzazione del prodotto
- Se invece effettuato all'inizio dello sviluppo di un prodotto, può guidare lo sviluppo ad un'ottimizzazione del prodotto finale a seconda del mercato dove deve andare…

- L'HTA è da sempre insegnata e studiata in economia e medicina, mentre da poco sta entrando nel mondo dell'ingegneria clinica
  - invece l'ingegnere clinico è spesso quello che individua il bisogno di una nuova tecnologia e / o la sviluppa…

Early stage HTA



e-HTA



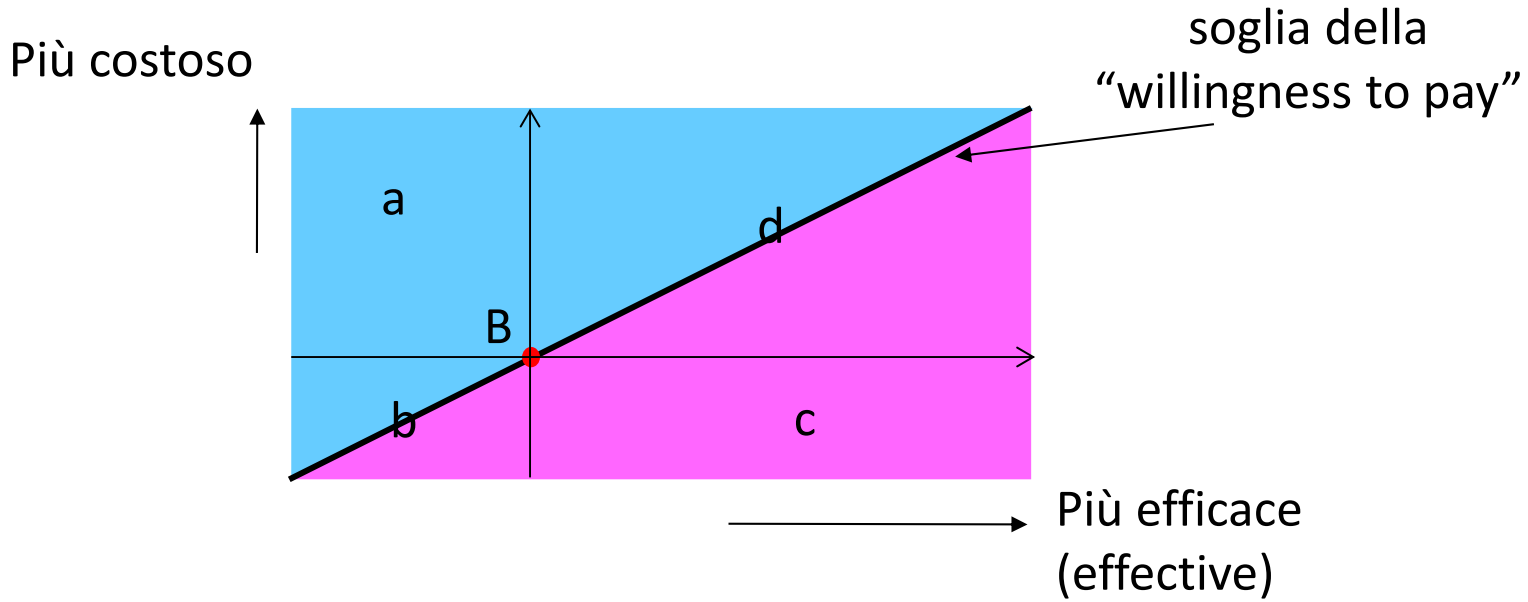
Efficacy: quanto è in grado la mia soluzione di risolvere un dato problema

Efficency: quanto è efficiente la mia soluzione

$$\text{Efficency} = \frac{\text{Efficacy}}{\text{Costi}} = \frac{\text{10 vite}}{\text{Costi}}$$

In un mondo con scarse risorse i costi sono importanti, perché se si risparmia si possono soddisfare altri bisogni…

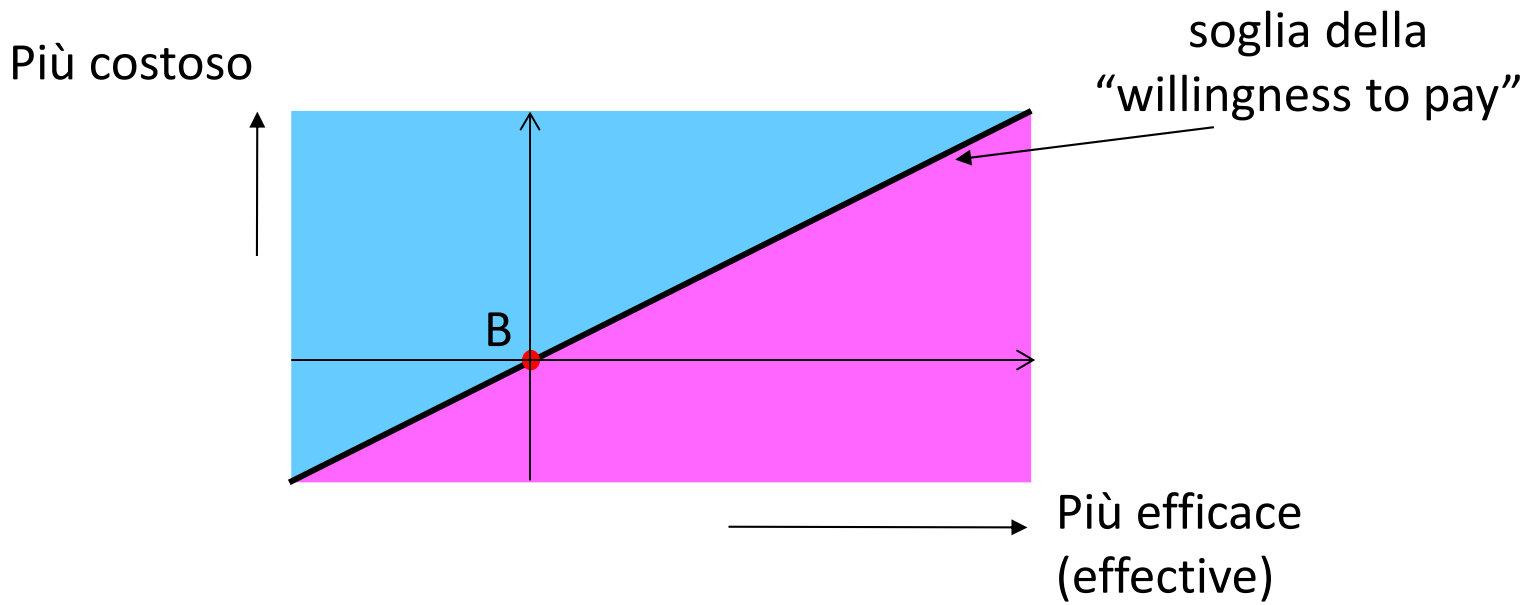
Metodo standard



B = benchmark con cui ci si confronta; gli assi definiscono il costo e l’efficacia del benchmark (punto di riferimento dell’analisi

La linea diagonale rappresenta la soglia della “willingness to pay” ovvero quanto “il sistema” (investitori, acquirenti, strutture ospedaliere) sono disposti a pagare per la soluzione del problema.
La nuova soluzione potrebbe anche essere più costosa del benchmark, ma se più efficace e sotto la soglia del willingness to pay avrà comunque possibilità nel mercato…

Metodo standard



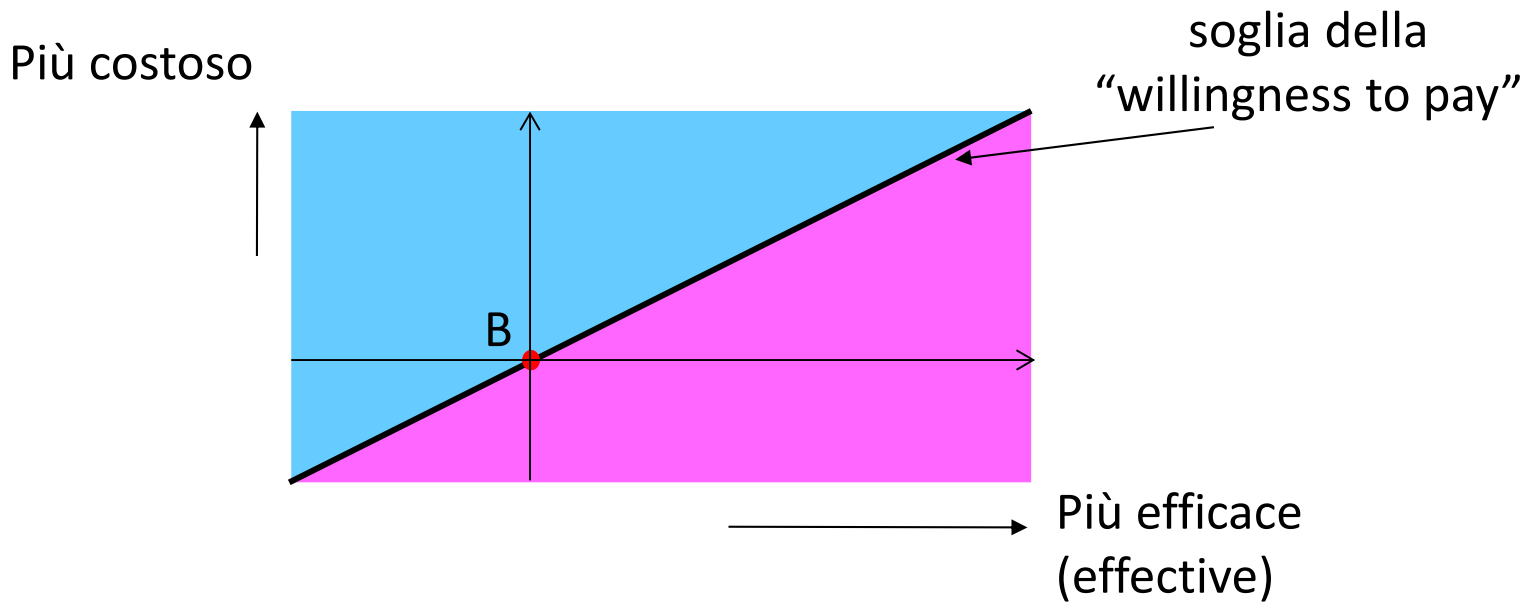
a = la mia soluzione è meno efficace e più costosa di B

b = la mia soluzione è meno efficace e meno costosa di B

c = la mia soluzione è più efficace e meno costosa di B

d = la mia soluzione è più efficace e meno costosa di B

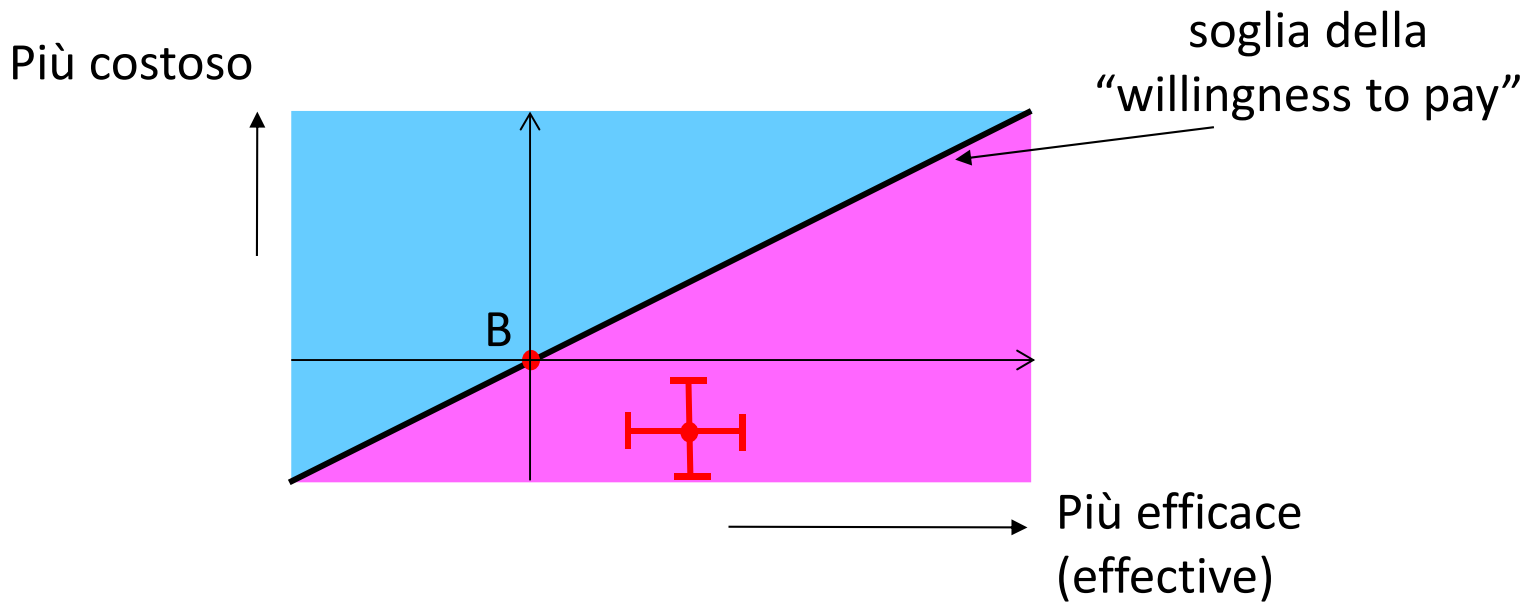
Metodo standard



Il diagramma non è statico, perché anche la posizione del benchmark varia nel tempo… (soprattutto se è un dispositivo medico, i farmaci sono più stabili)

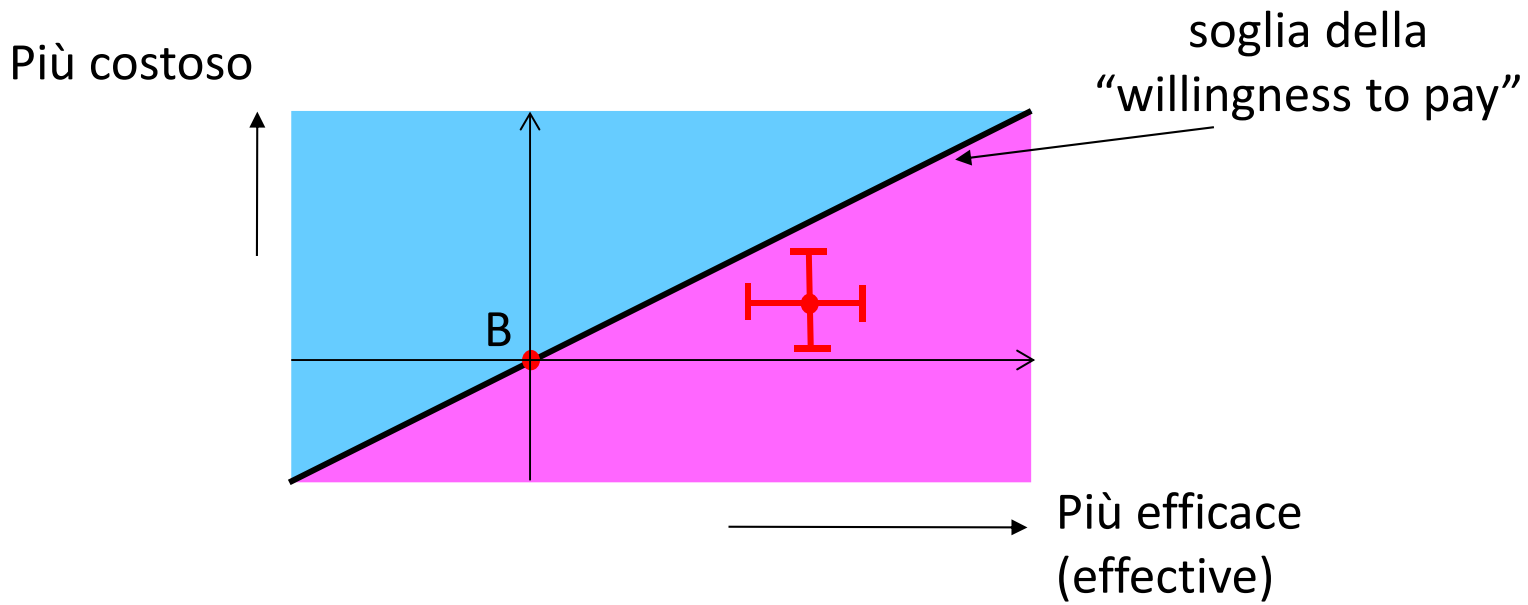
Collocamento della nuova tecnologia nel diagramma… con HTA... quindi indicazioni di come ci si deve muovere nello sviluppo, e.g. ridurre i costi, o migliorare l’efficacia...

Metodo standard - esempi



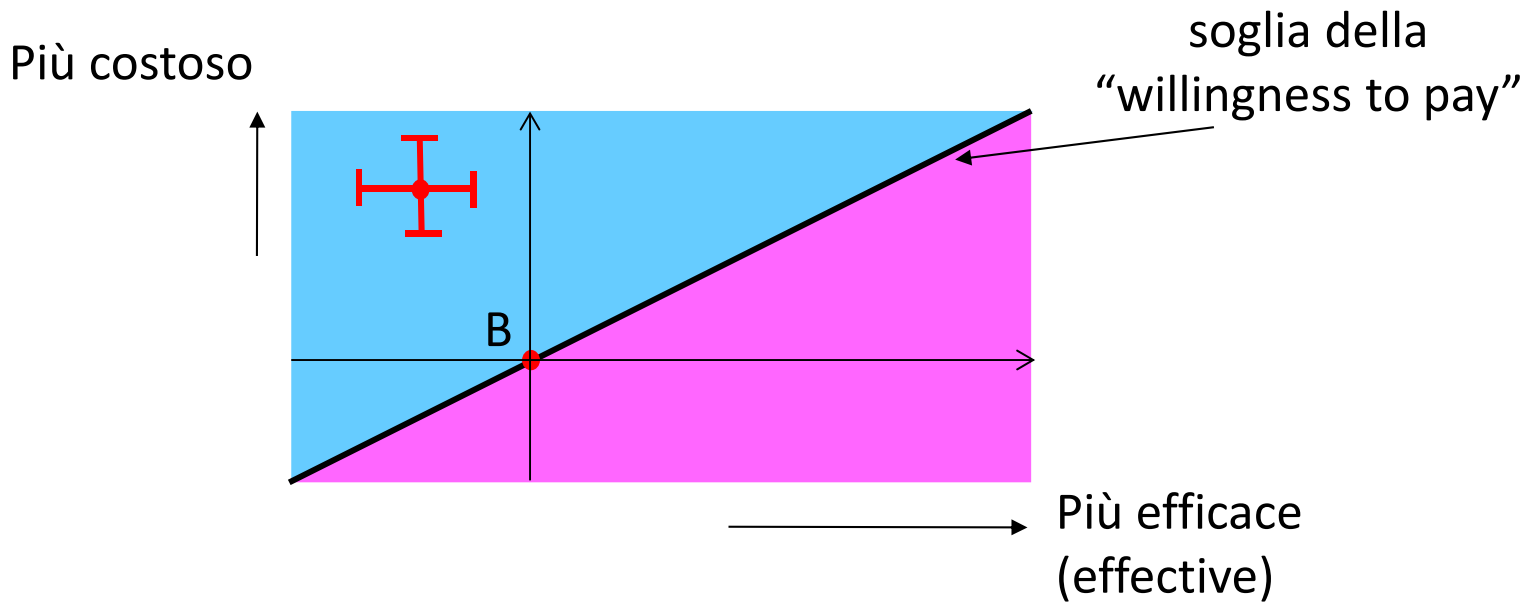
Qui si è in zona sicura, con costi minori del benchmark e anche migliore efficacia

Metodo standard - esempi



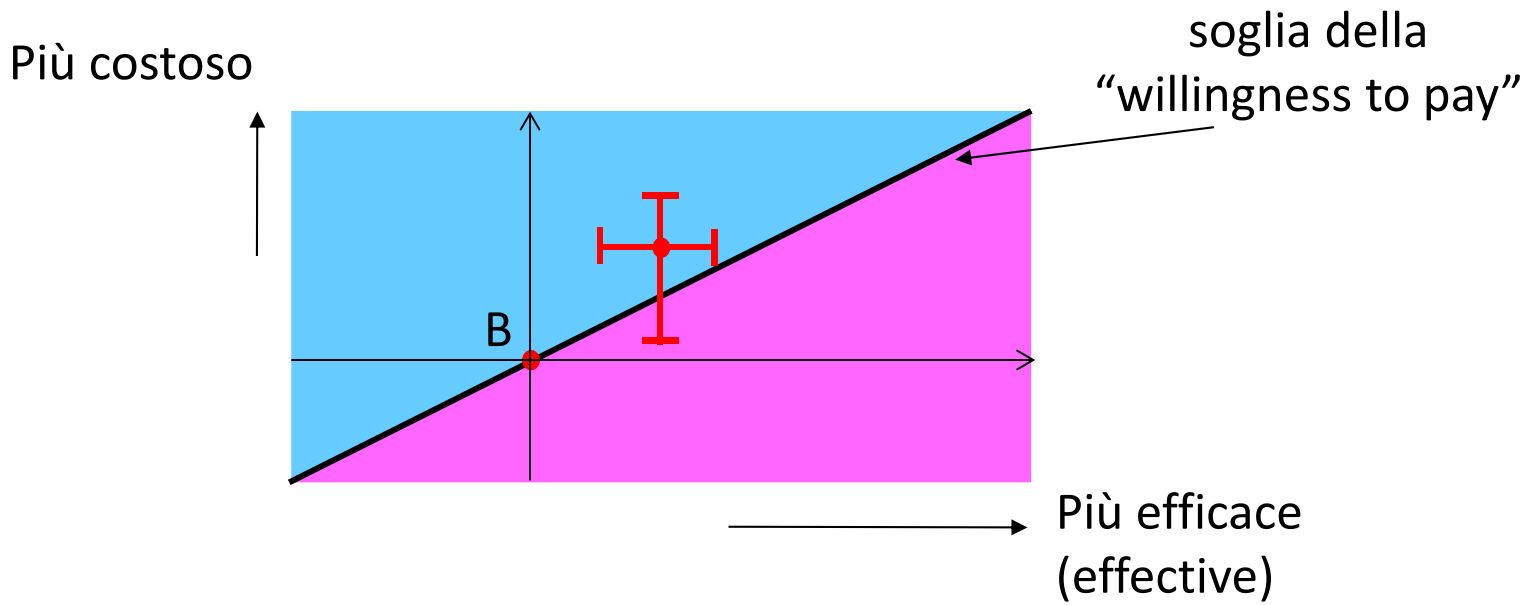
E’ comunque più efficace e sotto la willingness to pay…

Metodo standard - esempi



Qui l‘idea non va per niente bene..

Metodo standard - esempi



Bisogna ridurre l’incertezza e possibilmente ridurre i costi…

Metodi standard

I metodi standard sono stati sviluppati inzialmente per i farmaci.. bisogna stare attenti alla loro applicazione ai dispositivi medici perché ci sono grosse differenze

Devices	VS	Drug
Principal action		
Other than principally drugs		Pharmaco./Immunologic/Metabolic
Mechanical/Electromagnetic/Materials		Chemical based
Product life cycle		
Short life cycle		Long life cycle
Constantly evolving components/parts		Unchanging compound
Clinical evaluation		
Difficult to blind (no placebo)		Easy to blind
Multiple end users		Usually one end users
Long learning curve		Short learning curve
Strongly dependent by settings/users		Less dependent by settings/users
Complex to standardize for RCT		Easy to standardize for RCT
Use issues		
User-dependent efficacy		Efficacy is less user-dependent
Often require intensive training		Usually do not require training
Complication decrease with use		Complication increase with use
Diversity		
Mainly small companies/few large co.		Mainly large multinationals
Diagnostic or therapeutic		Therapeutic
Costs		
Varying overheads/slow return		High overheads with quicker return
Higher distribution costs		Lower distribution costs
Higher maintenance/installation costs		No maintenance/installation

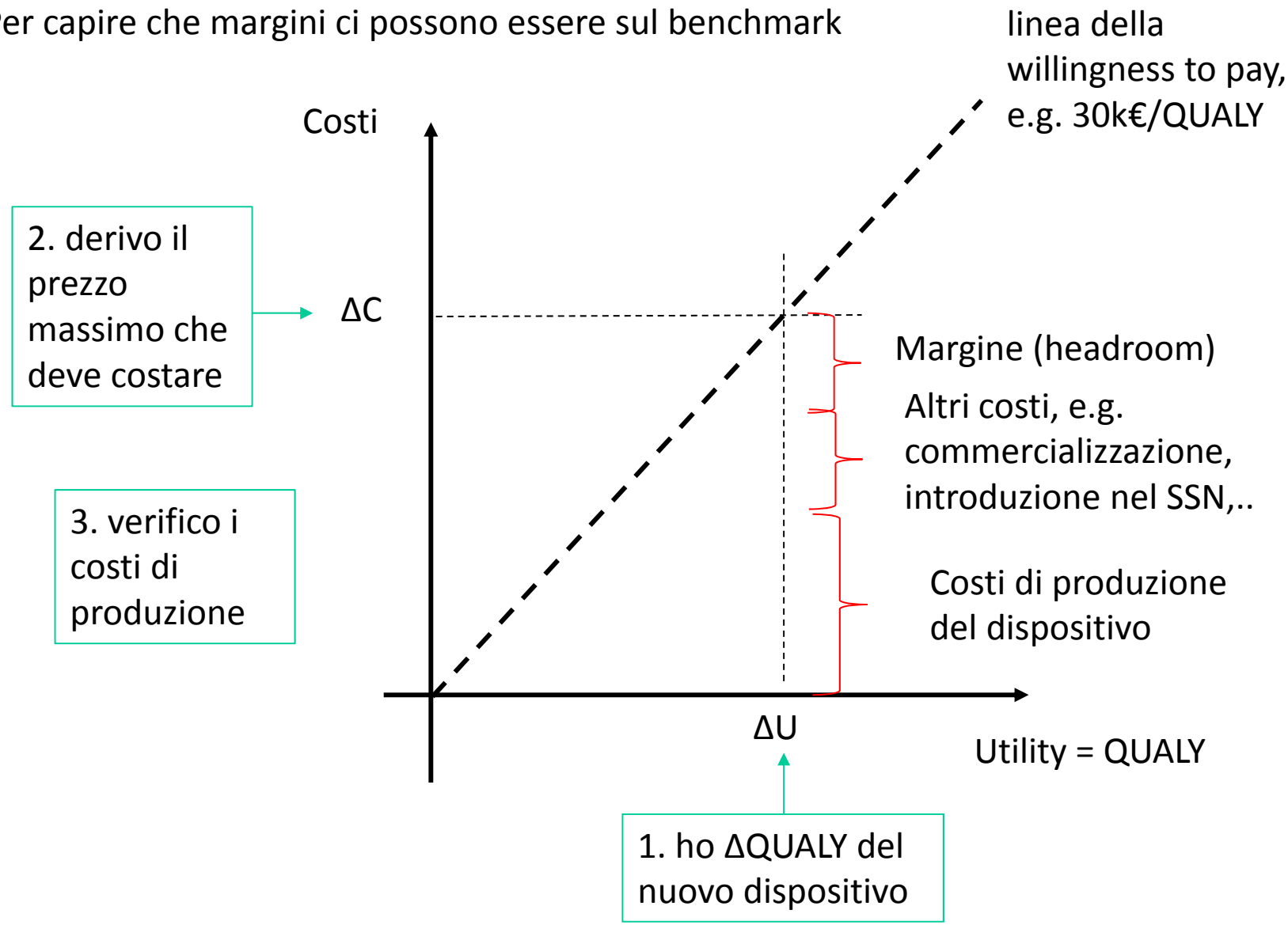
Metodi per eHTA

- **Headroom Analysis (HA)**
  - Assumendo un dato beneficio per il paziente rispetto alla tecnica attualmente in uso…

  .....quale è il massimo costo che deve avere il nuovo dispositivo per essere efficiente?
  - Vale l'investimento di risorse?
  - C'è un ragionevole margine di guadagno?
- **Modelli statistici predittivi**
  - Volendo sviluppare un nuovo prodotto per definirne la complessità di sviluppo, analisi basata sulla migliore conoscenza attuale
  - e.g. sistema di home monitoring, quanto deve essere complesso (quanti parametri deve registrare, ogni quanto tempo...), quale è la popoalzione di riferimento perché sia competitivo con le tecniche di monitoraggio attuali?
- **Analytic Hierarchy Process (AHP)**
  - La soluzione che si propone risponde ai bisogni di una determinata "popolazione"?
  - Per rispondere si sviluppa un'analisi analoga alla HTA in modo da codificare i bisogni, la loro importanza gli uni rispetto agli altri e così confrontare la nuova proposta con i metodi già esistenti
- **Modelli di Markov**
  - Assumendo che il dispositivo abbia un dato beneficio (e.g. riduce di un tot% la mortalità), sarà efficiente dal punto di vista dei costi con una certa probabilità?
  - L'analisi simula in modo statistico la relazione costi-efficacia, sempre confrontando diverse soluzioni (la nuova e l'attuale)

Headroom analysis

Per capire che margini ci possono essere sul benchmark



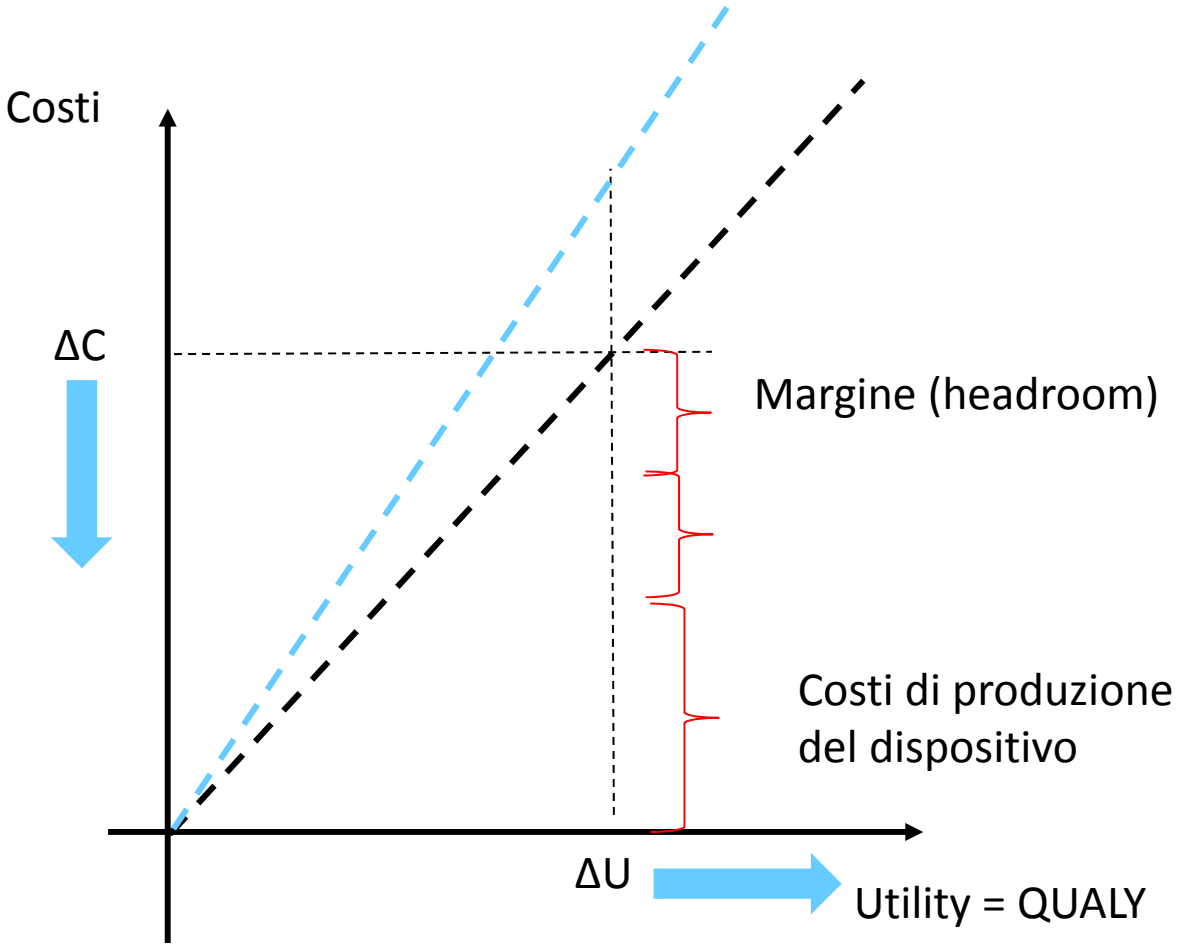
Headroom analisi

Trovato il margine, la prima domanda è **se è sufficiente**… (se non ce ne è è meglio ricominicare da capo...)

.. quindi si può ragionare se si può migliorare l'efficienza del dispositivo, ad esempio meglio focalizzando la sua applicazione (ad esempio definendo meglio la "popolazione obiettivo" della terapia).

oppure vedere se si possono ridurre i costi di produzione,

o infine, se esiste una diversa applicazione clinica del dispositivo nella quale la willingness to pay è maggiore…



Predictive statistical methods

- Individuato un “bisogno” a cui si vuole dare una risposta innovativa, confronto dell’idea con lo stato dell’arte attuale attraverso analisi di letteratura individuando i parametri importanti dell’analisi
- e.g. caso di monitoraggio a distanza (home monitoring) si deve definire ogni quanto registrare e trasmettere i dati, quali dati, quale è la popolazione target (se solo già malati o anziani in genere..)
  - vd efficacia vs severità della malattia
  - vd efficacia vs complessità del sistema
- L’analisi statistica è effettuata supponendo un certo numero di eventi (info da data-base) in una data popolazione e vedendo costo / utilità del nuovo sistema rispetto a quello esistente

Analytic Hierarchy Process (AHP)

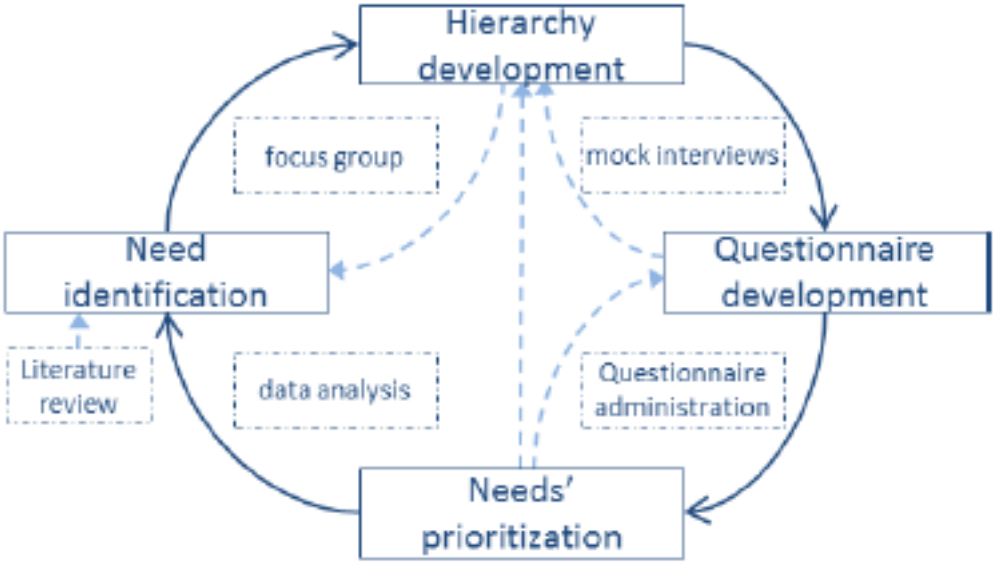
This hierarchical approach allows the construction of a consistent framework for step-by-step deci-sion-making [2], breaking a complex problem into many small less-complex ones that decision-makers can more eas-ily deal with[3]. This paradigm, known as *divide et impera* [4] (divide and rule) and widely investigated in medicine [5, 6], has been demonstrated to be effective in healthcare deci-sion-making[7].

AHP is a multi-dimensional, multi-level and multifactorial decision-making method based on the idea that it is possible to prioritize elements by: grouping them into meaningful categories and sub-categories; performing pairwise comparisons; defining a coherent framework of quantitative and qualitative knowledge; measuring intangible domains. The AHP method is detailed described in [8, 9] ac-cessible respectively via gold and green open access. The need prioritization via AHP method is performed in 9 stage:

1. *Needs identification*: focus-group of 1-2 domain experts;
2. *Design of a tree-of-needs* with nodes (categories of needs), sub-nodes (sub-categories of needs) and leaf (needs): this involves 1 domain expert and 1 researcher experienced in the AHP.
3. *Tree piloting*. This involves “n” domain expert/s, where n is dynamically established according to variability among experts’ opinions.
4. *Questionnaires’* development (1 AHP expert).
5. *Questionnaire piloting*. This involves a small group of se-lected responders (from 1 to 3), with experience of participation in user needs elicitation studies.
6. Final *tree and questionnaire development* (1 AHP expert, 1 domain expert and 1 experienced elicitor).
7. Questionnaire submission to the appropriate number of re-sponders.
8. Data analysis end results presentation (1 expert of AHP)
9. Results interpretation and discussion (1 expert of AHP, 1 domain expert, 1 elicitor and some users).

AHP: definizione del problema

After defining the problem (research question), the needs that a health technology has to satisfy are identified and organized in meaningful categories, creating a hierarchy of needs. According to the hierarchy, a series of questionnaires are developed.



Analytic Hierarchy Process (AHP) to select the surgical approach in hernia repair: laparoscopic (TAPP) versus open surgery. Study design and piloting.

L. Pecchia[1], G. Merola[2], M. Sodo[2], U. Bracale[2]

AHP: Costruzione gerarchia

- A literature review was performed as described in [1]. From this systematic review and after a focus group with three surgeons with experience of both LHR and OHR, a hierarchy of 22 needs, organized in 10 sub-categories and 3 categories was developed

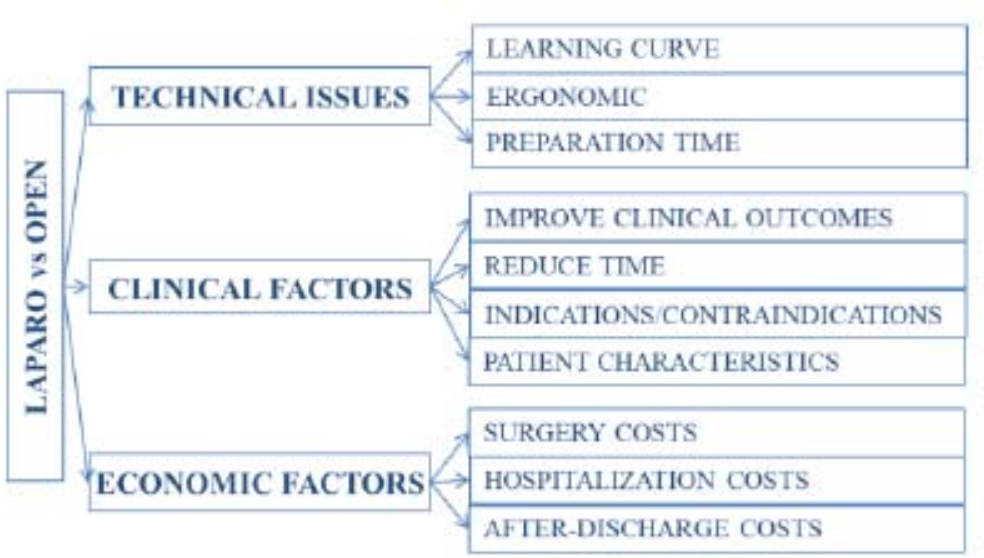


Table 1 category relative importance (C.R.>0.1)

Category of needs	weight
Clinical factors	50%
Economic factors	25%
Technical issues	25%

Table 1 reports the global importance (weight) of each category of need expressed in %. The three surgeons judged the clinical factors twice more important than the economic and the technical ones.

AHP: Pesi dei diversi elementi

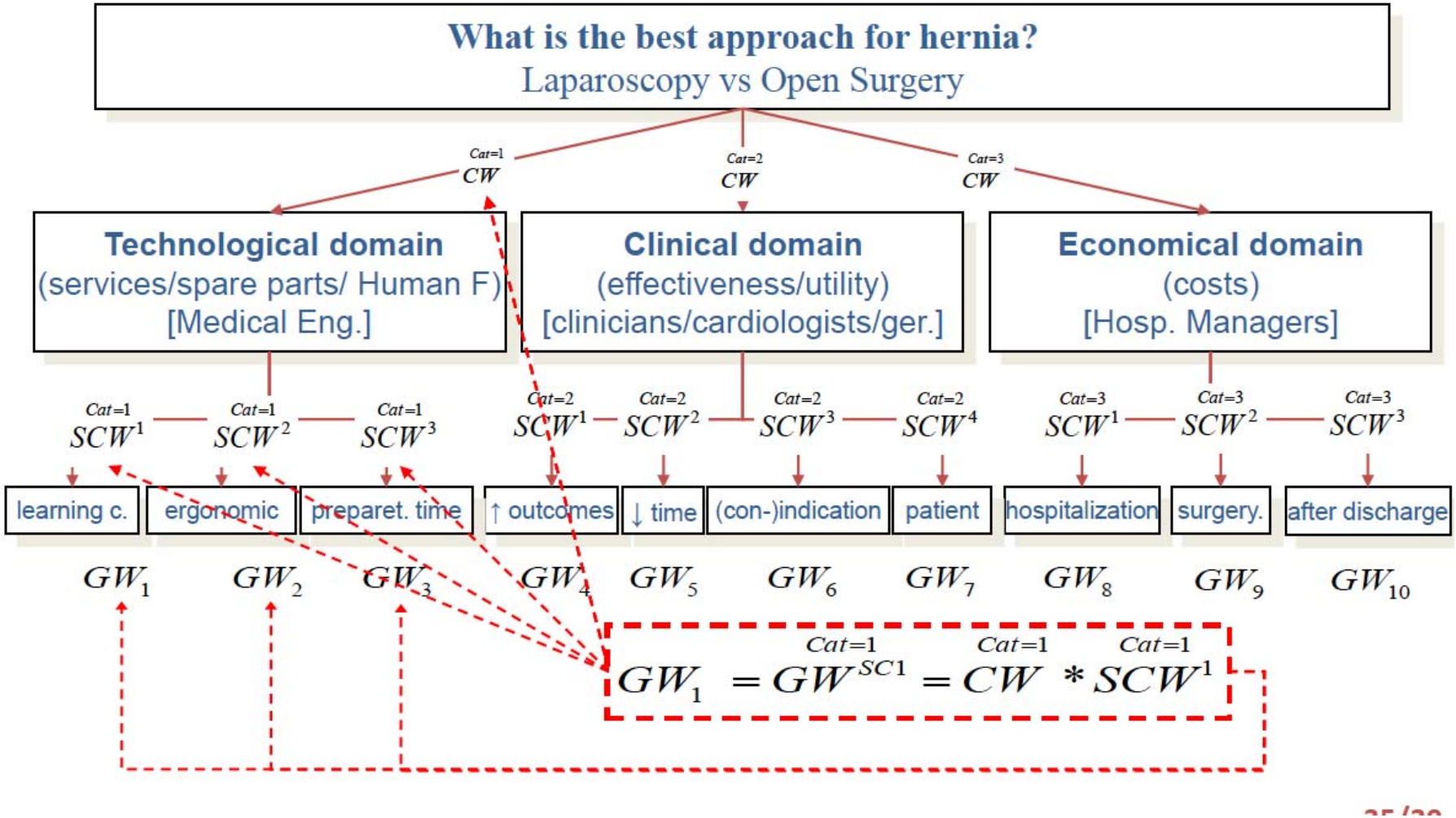
Table 2 reports the local and the global importance of each subcategory of needs. The global importance is the sub-category local weights multiplied by the weight of its father node (category). For instance the global weight of "improve clinical outcome" (15%) is the product of its local weight (30%) among all the leafs of the father node (Clinical fac-tors), multiplied per the weight of the father node (50%).

Table 2 category relative importance (C.R>0.1)

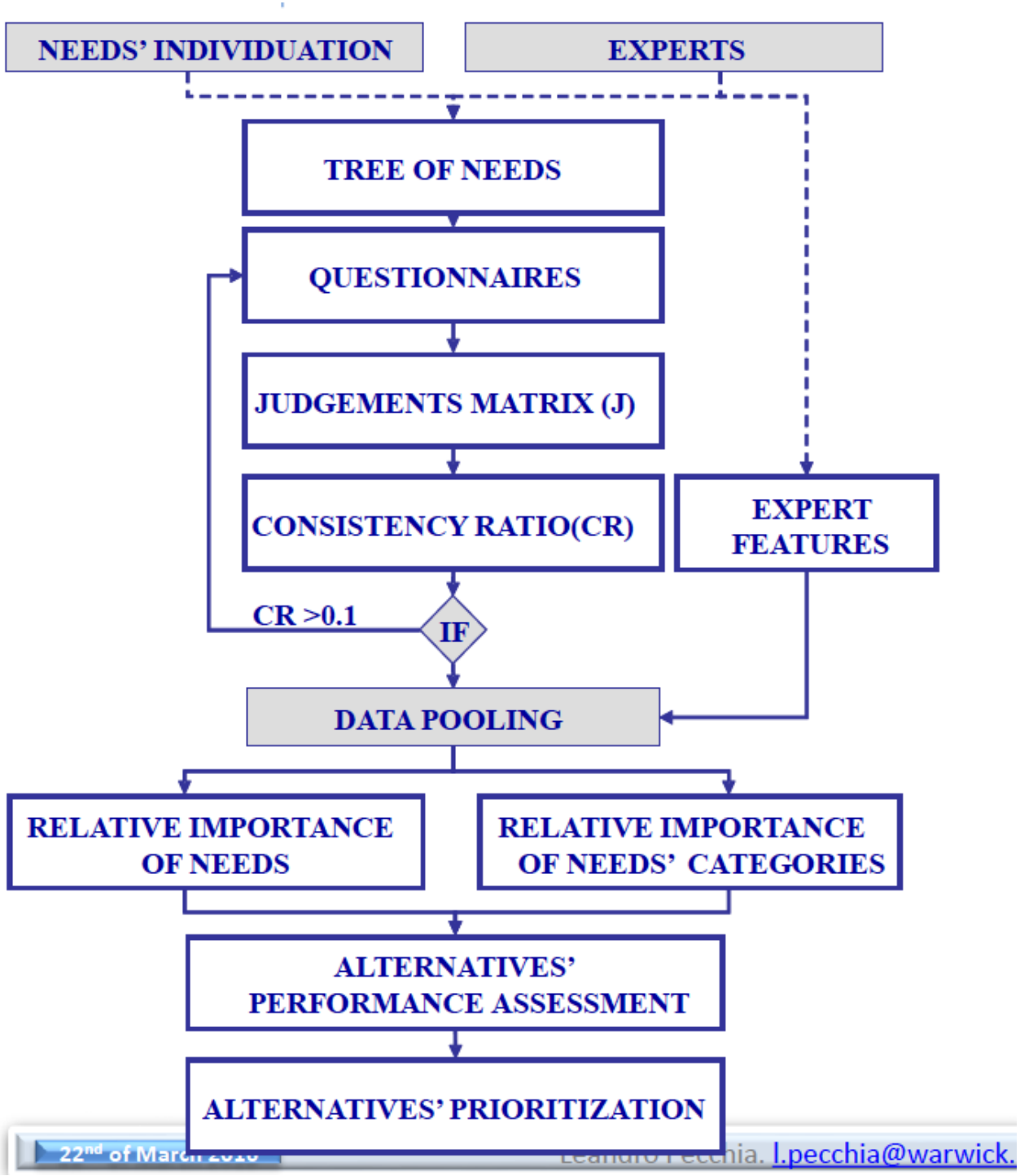
Category of needs	Local weight	Global weight
Clinical factors		
Improve clinical outcomes	30%	15%
Reduce time	10%	5%
Patient characteristics	30%	15%
indications/contraindications	30%	15%
Economic factors		
Reduce surgery costs	20%	5%
Reduce hospitalization costs	49%	12%
Reduce after-discharge costs	31%	8%
Technical issues		
Learning curve	53%	13%
Ergonomic	33%	8%
Preparation time	14%	4%

Regarding the global importance of the subcategories, 5 out of 10 resulted to be significantly more important, absorb-ing the 70% of the global importance. It is significant that 2 out of those 5 did not fall into the most important category (clinical factor), reflecting that the importance of the subcat-egories was not masked by the one of father nodes.

AHP: esempio di gerarchia con i pesi



AHP: Gerarchia



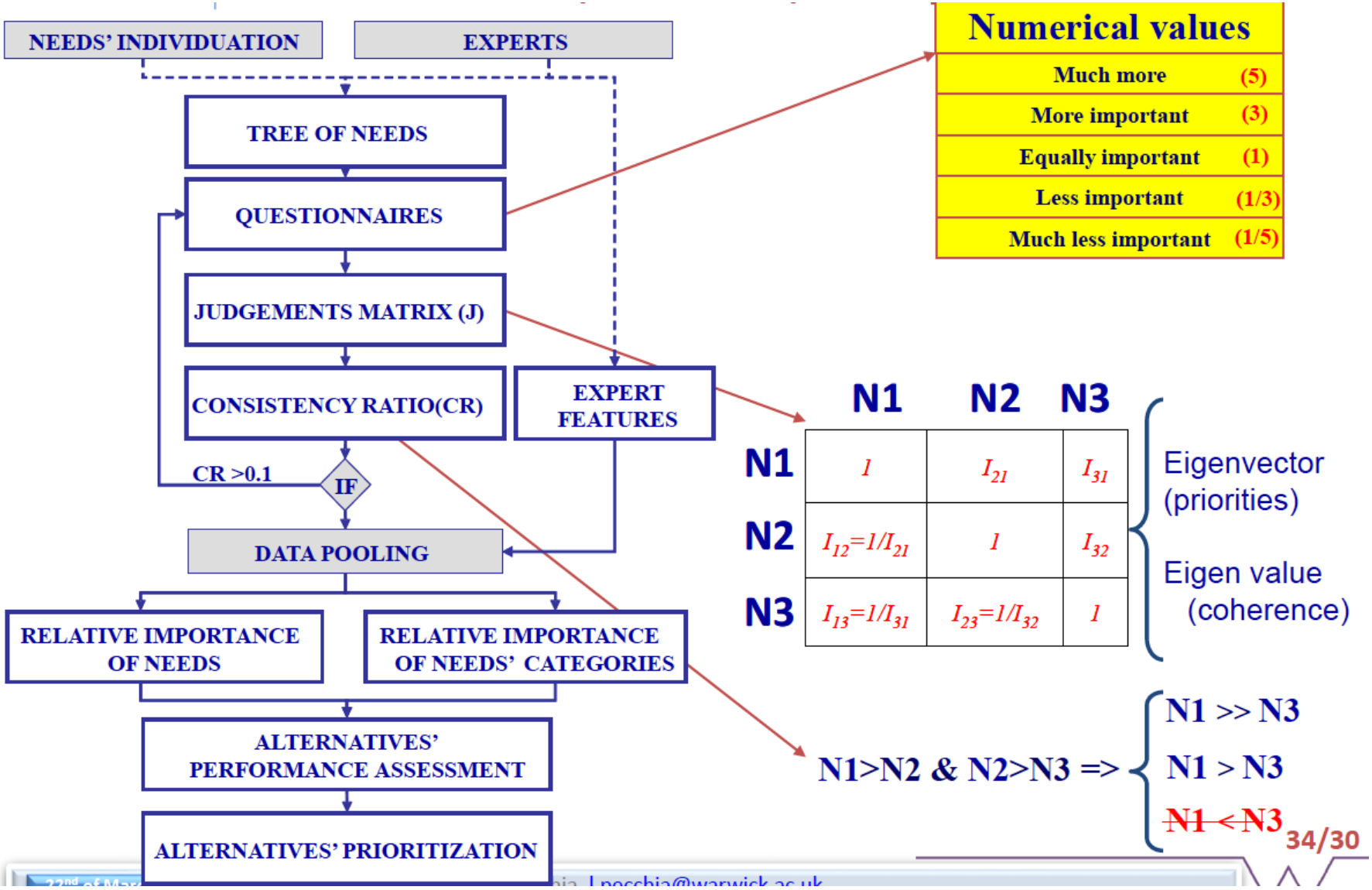
AHP: Questionario

For each node of the hierarchy the 3 surgeons were required to compare pairs of elements falling in the same node (either category of sub-category), using questionnaires

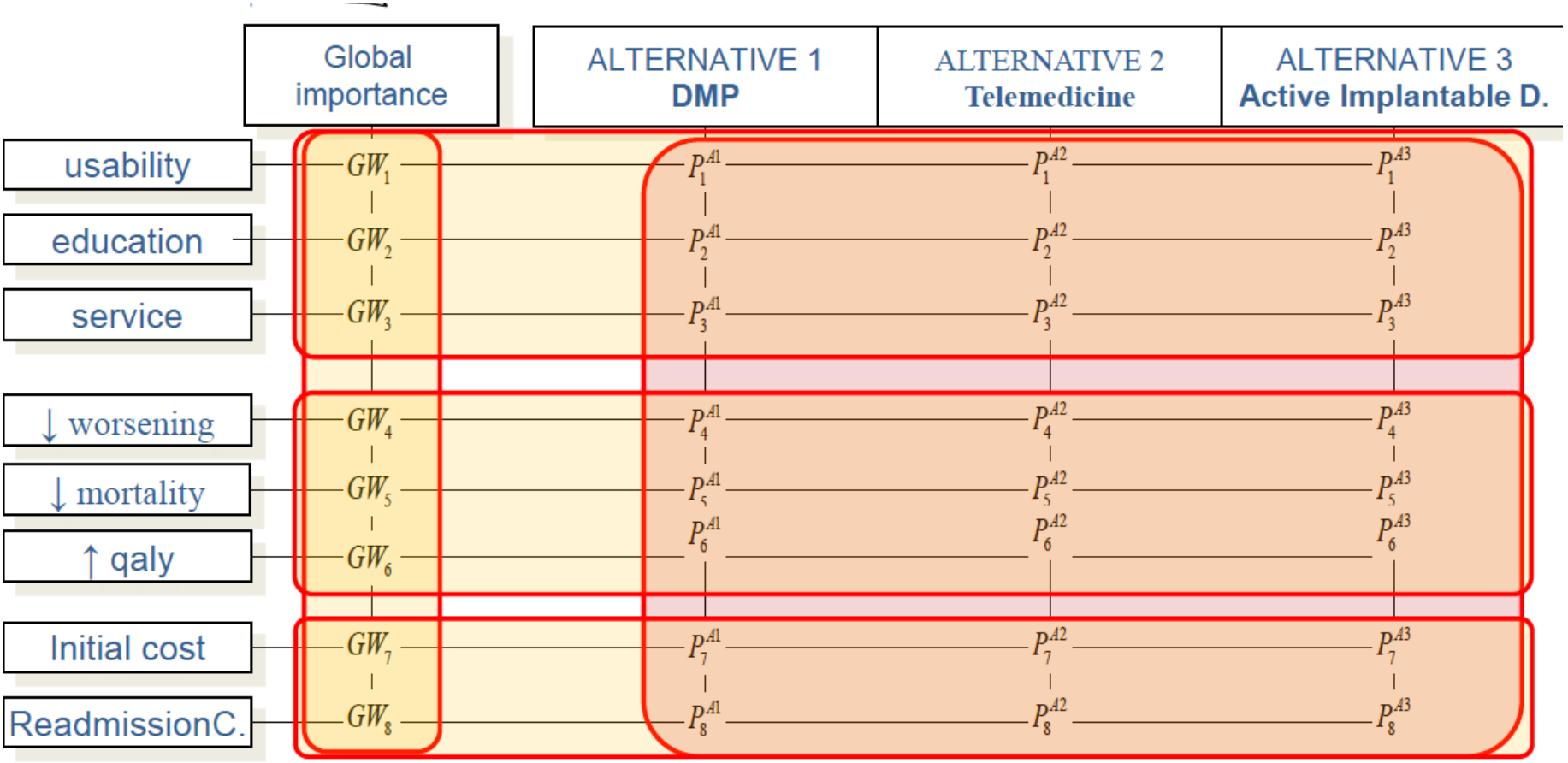
According to your experience, how important is each need on the left compared with each one on the right?

Need 1 (↓ mortality)	Is:	*much more*	*more*	*equally*	~~*less*~~	*much less*	important hen	***Need 2 (↓ Pz. worsening)***
Need 2 (↓ Pz. worsening)	is:	*much more*	*more*	~~*equally*~~	*less*	*much less*	important hen	***Need 3 (↑ QALY)***
Need 3 (↑ QALY)	is :	~~*much more*~~	*more*	*equally*	*less*	*much less*	important hen	***Need 1 (↓ mortality)***

AHP: Controllo congruenza



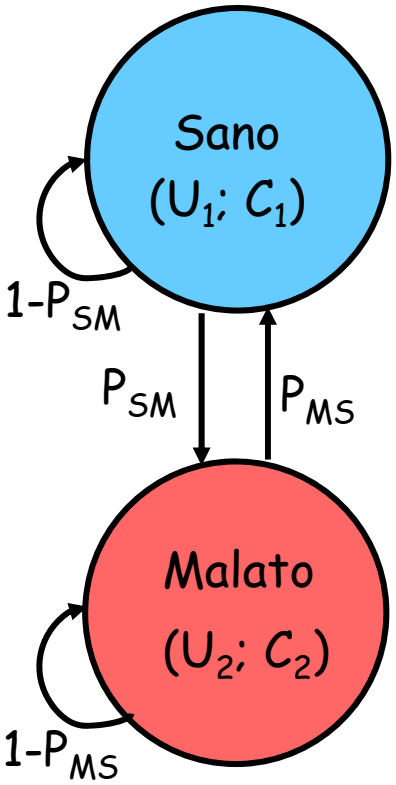
AHP: Assegnazione valore finale



$$Global\ PerfomanceAlternative_j = \sum_{i=1}^{8} GW_i * P_i^{Aj}$$

Modelli di Markov

- The model assumes that the patient is always in one of a finite number of states of health referred to as Markov states.
- All events of interest are modelled as transitions from one state to another.
- The time horizon of the analysis is divided into equal increments of time, referred to as Markov cycles. During each cycle, the patient may make a transition from one state to another.
- Each state is assigned a utility, and the contribution of this utility to the overall prognosis depends on the length of time spent in the state. The utility that is associated with spending one cycle in a particular state is referred to as the incremental utility.
- The net probability of making a transition from one state to another during a single cycle is called a transition probability.
- Evaluation of a Markov process yields the average number of cycles (or analogously, the average amount of time) spent in each state.

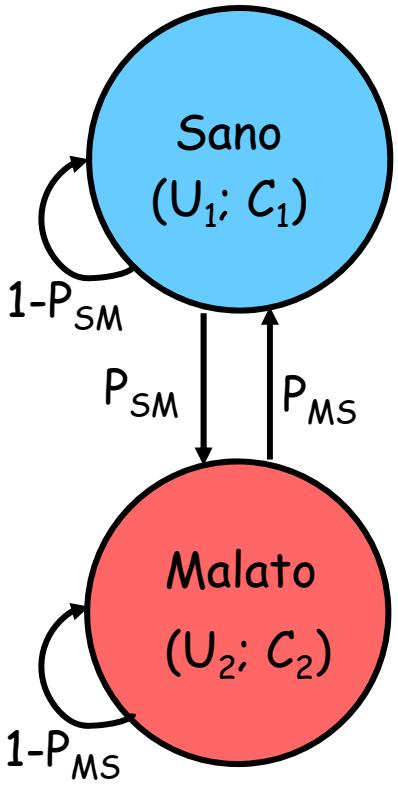


Sonnenberg, Beck, 1993

Modelli di Markov

- e.g., if the incremental utility of the DISABLED state is 0.7, then spending the cycle in the DISABLED state contributes 0.7 quality-adjusted cycles to the expected utility.
- Utility accrued for the entire Markov process is the total number of cycles spent in each state, each multiplied by the incremental utility for that state.

$$Expected \quad utility = \sum_{s=1}^{n} (t_s \cdot u_s)$$



Proprietà del modello di Markov

- In order for this model to represent a Markov process, one additional restriction applies. This restriction, sometimes referred to as the Markovian assumption (or the Markov property) specifies that the behavior of the process subsequent to any cycle depends only on its description in that cycle.

  That is, the process has no memory for earlier cycles.
- Put another way, all patients in the DISABLED state have the same prognosis regardless of their previous histories.
- The Markovian assumption is not followed strictly in medical problems. However, the assumption is necessary in order to model prognosis with a finite number of states.

Stati

- In order for a Markov process to terminate, it must have at least one state that the patient cannot leave. Such states are called absorbing states because, after a sufficient number of cycles have passed, the entire cohort will have been absorbed by those states. (*nb. esistono Markov processes senza "stati assorbenti"*)
- Temporary states are required whenever there is an event that has only short-term effects. Such states are defined by having transitions only to other states and not to themselves. Temporary states have two uses. The first use is to apply a utility or cost adjustment specific to the temporary state for a single cycle. The second use is to assign temporarily different transition probabilities.
- A special arrangement of temporary states consists of an array of temporary states arranged so that each has a transition only to the next. These states are called tunnel states because they can be visited only in a fixed sequence, analogous to passing through a tunnel. The purpose of an array of tunnel states is to apply to incremental utility or to transition probabilities a temporary adjustment that lasts more than one cycle.

Tipi di processi di Markov

- Markov processes are categorized according to whether the state-transition probabilities are constant over time or not.
- A special type of Markov process in which the transition probabilities are constant over time is called a Markov chain.
- In the most general case, the transition probabilities in a Markov model vary with time. An obvious example is the probability of death, which increases as the cohort ages.

- Incremental utilities, like transition probabilities, may vary with time

Soluzione processi di Markov

- The Markov process is completely defined by the probability distribution among the starting states and the probabilities for the individual allowed transitions. For a Markov model of n states, there will be n^2 transition probabilities. When these probabilities are constant with respect to time, they can be represented by an n x n matrix, as shown in table 1. Probabilities representing disallowed transitions will, of course, be zero.

- This matrix, called the P matrix, forms the basis for the fundamental matrix solution of Markov chains described in detail by Beck and Pauker (1983).

Table 1 • P Matrix

		To		
		WELL	DISABLED	DEAD
From	WELL	0.6	0.2	0.2
	DISABLED	0	0.6	0.4
	DEAD	0	0	1

Valutazione probabilità transizione

- Le probabilità di transizione possono essere derivate dalla letteratura clinica o da una valutazione effettuata da esperti.
- Normalmente, la letteratura clinica esprime la transizione da uno stato ad un altro mediante il concetto di tasso (*rate*): il tasso varia tra 0 ed infinito ed è espresso per unità di tempo (e.g. «la mortalità dovuta ad una malattia X è del 2% ad anno»).
- D'altro canto, le probabilità variano tra 0 ed 1 e il tempo è insito in modo implicito nel loro valore.

Per un dato tasso r, la probabilità che il passaggio di stato avvenga entro un intervallo temporale lungo t-unità di tempo, è data da:

$$P(t) = 1 - e^{-rt}$$

e.g.

su 100 pazienti, 70 si ammalano entro 3 anni. Ovvero, in 3 anni ci sono state 70 transizioni tra lo stato sano e quello malato, o (70/100/3=) 0.233 transizioni per paziente per anno (tasso di morbidità).

Se si sceglie per il ciclo di Markov una lunghezza di un anno, la probabilità di transizione da associare al passaggio sano – malato sarà: $P(t) = 1 - e^{-0.233 \cdot 1} = 0.208$

Se invece si sceglie un ciclo di un mese:

$$P(t) = 1 - e^{-0.233 \cdot 1/12} = 0.019$$

Soluzione dei processi di Markov

I modelli di Markov possono essere analizzati con tre diverse tecniche:

- Soluzione matriciale (solo se le probabilità sono costanti)
- Simulazione cohorte
- Simulazione Monte-Carlo

Soluzione matriciale

- Per questo tipo di analisi si parte dalla matrice delle probabilità di transizione

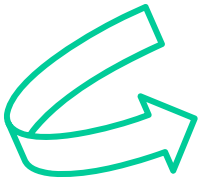
Table 1 • P Matrix

		To		
		WELL	DISABLED	DEAD
From	WELL	0.6	0.2	0.2
	DISABLED	0	0.6	0.4
	DEAD	0	0	1

- Di questa si considera solo la parte che contiene le probabilità di transizione tra stati non assorbenti, ovvero rappresenta la probabilità di non essere assorbito
- Elaborando questa parte di matrice con pochi passaggi matematici si risolve il problema….

Soluzione matriciale

		To:	
		Non absorbing states	Absorbing states
From:	Non absorbing states	Q	R
	Absorbing states	0	I



e.g.

		To:		
		Well	Ill	Dead
From:	Well	0.3	0.5	0.2
	Ill	0	0.5	0.5
	Dead	0	0	1

Soluzione matriciale

- Si valuta la matrice N, ottenuta sottraendo Q dalla matrice identità e quindi calcolando l'inversa:

$$N=(I-Q)^{-1}$$

- Il calcolo è l'equivalente algebrico della valutazione del reciproco della probabilità di transizione, e come tale ha nelle colonne il tempo medio di permanenza in uno stato prima dell'assorbimento, partendo dallo stato indicato nella riga
- Pertanto la matrice N rappresenta la soluzione del problema, equivalentemente alle altre due soluzioni che però hanno bisogno (come si vedrà di molti più calcoli)
- Sommando gli elementi di riga di N si ottiene il tempo di vita atteso per lo stato inziale individuato dalla riga. Moltiplicando gli elementi della matrice per le utilità (o i costi) si otterrà il valore totale
- Si ha anche la matrice varianza, data da

$$V=N(2N'-I)-N^{(2)}$$

con N' ottenuta da N azzerando tutti gli elementi tranne quelli della diagonale principale, e $N^{(2)}$ ottenuta sostituendo ad ogni elemento di N il suo quadrato

Soluzione matriciale: esempio

$$Q = \begin{bmatrix} 0.3 & 0.5 \\ 0 & 0.5 \end{bmatrix}$$

$$N = \left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} - \begin{bmatrix} 0.3 & 0.5 \\ 0 & 0.5 \end{bmatrix} \right)^{-1} = \begin{bmatrix} 1.43 & 1.43 \\ 0 & 2.00 \end{bmatrix}$$

$$V = \begin{bmatrix} 1.43 & 1.43 \\ 0 & 2.00 \end{bmatrix} \left(2 \begin{bmatrix} 1.43 & 0 \\ 0 & 2.00 \end{bmatrix} - \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \right) - \begin{bmatrix} 1.43^2 & 1.43^2 \\ 0 & 2.00^2 \end{bmatrix} =$$

$$= \begin{bmatrix} 0.62 & 2.25 \\ 0 & 2.00 \end{bmatrix}$$

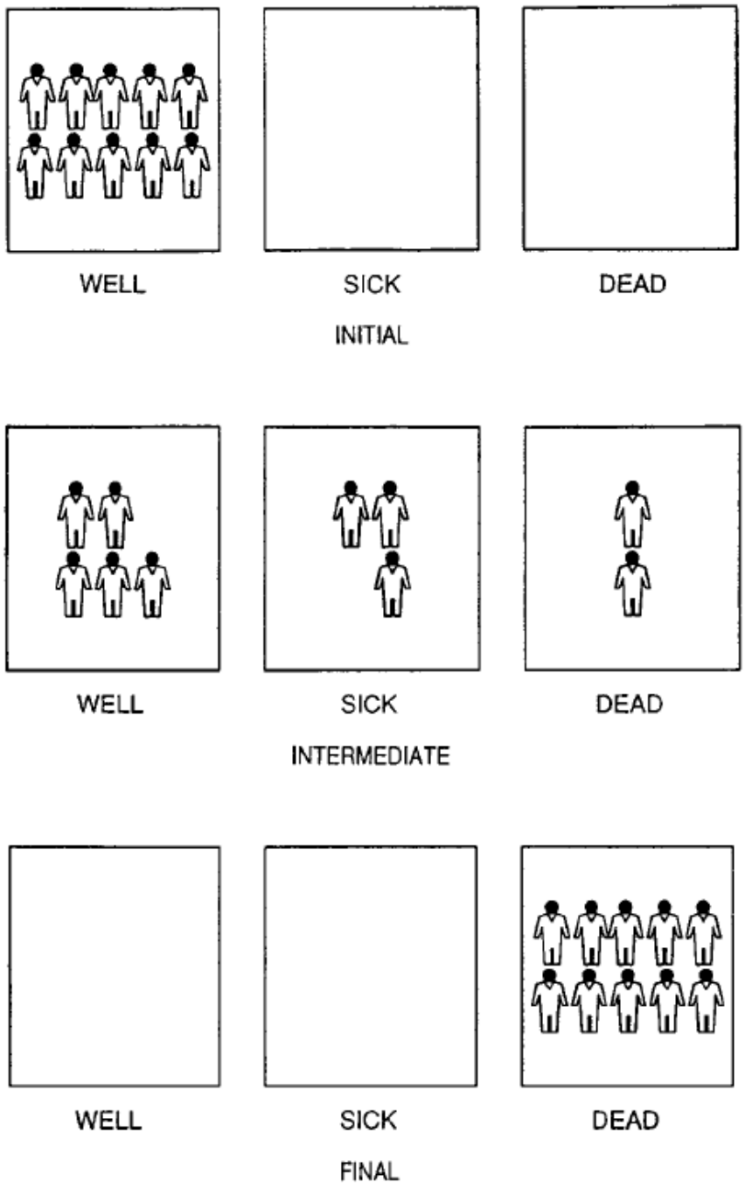
Guardando N si conclude che se lo stato iniziale è “well” l’aspettativa di vita sarà 1.43+1.43=2.86 cicli

Simulazione coorte

- The Markov cohort simulation is the most intuitive representation of a Markov process.
- The simulation considers a hypothetical cohort of patients beginning the process with some distribution among the starting states.
- For each cycle, the fraction of the cohort initially in each state is partitioned among all states according to the transition probabilities specified by the P matrix.
- The utility accrued for the cycle is referred to as the cycle sum and is calculated by the formula:

$$Cycle\ Sum = \sum_{s=1}^{n} f_s \cdot U_s$$

where n is the number of states, f_s is the fraction of the cohort in state s, and U_s, is the incremental utility of state s.



Simulazione coorte

- The cycle sum is added to a running total that is referred to as the cumulative utility.
- The cohort simulation can be represented in tabular form, as shown in table 2.
- A hypothetical cohort of 10000 patients begins in the WELL state. The second row shows the distribution at the end of the first cycle. In accordance with the transition probabilities specified in the P-matrix (table 1), 2000 patients (20% of the original cohort) have moved to the DISABLED state and another 2000 patients to the DEAD state. This leaves 6000 (60%) remaining in the WELL state.
- The fifth column in table 2 shows the calculation of the cycle sum, which is the sum of the number of cohort members in each state multiplied by the incremental utility for that state. For example, because the incremental utility of the DISABLED state is 0.7, the cycle sum during cycle 1 is equal to (6000 X 1) + (2000 X 0.7) = 7400.

Table 2 • Markov Cohort Simulation

Cycle	WELL	DISABLED	DEAD	Cycle Sum	Cumulative Utility
Start	10,000	0	0	—	—
1	6,000	2,000	2,000	7,400	7,400
2	3,600	2,400	4,000	5,280	12,680
•	•	•	•	•	•
•	•	•	•	•	•
23	0	1	9,999	7	23,752
24	0	0	10,000	<1	23,752
Total	15,000	12,500		23,752	23,752

Simulazione Monte Carlo

- The Monte Carlo simulation determines the prognoses of a large number of individual patients.
- Each patient begins in the starting state (i.e., the WELL state), and at the end of each cycle, a random-number generator is used together with the transition probabilities to determine in which state the patient will begin the next cycle.
- Just as for the cohort simulation, the patient is given credit for each cycle spent in a non-DEAD state and each state may be adjusted for quality of life.
- When the patient enters the DEAD state, the simulation is stopped.
- The process is repeated a very large number (on the order of 10^4) of times.
- Each trial generates a quality-adjusted survival time.
- After a large number of trials, these constitute a distribution of survival values. The mean value of this distribution will be similar to the expected utility obtained by a cohort simulation. However, in addition to the mean survival, statistical measures such as variance and standard deviation of the expected utility may be determined from this distribution.
- Of course, because we know for each simulated patient not only how long is spent in each non absorbing state but also when these non absorbing cycles occur, we could simulate the effects of changes in the utility of each state over time (Beck&Pauker 1983)

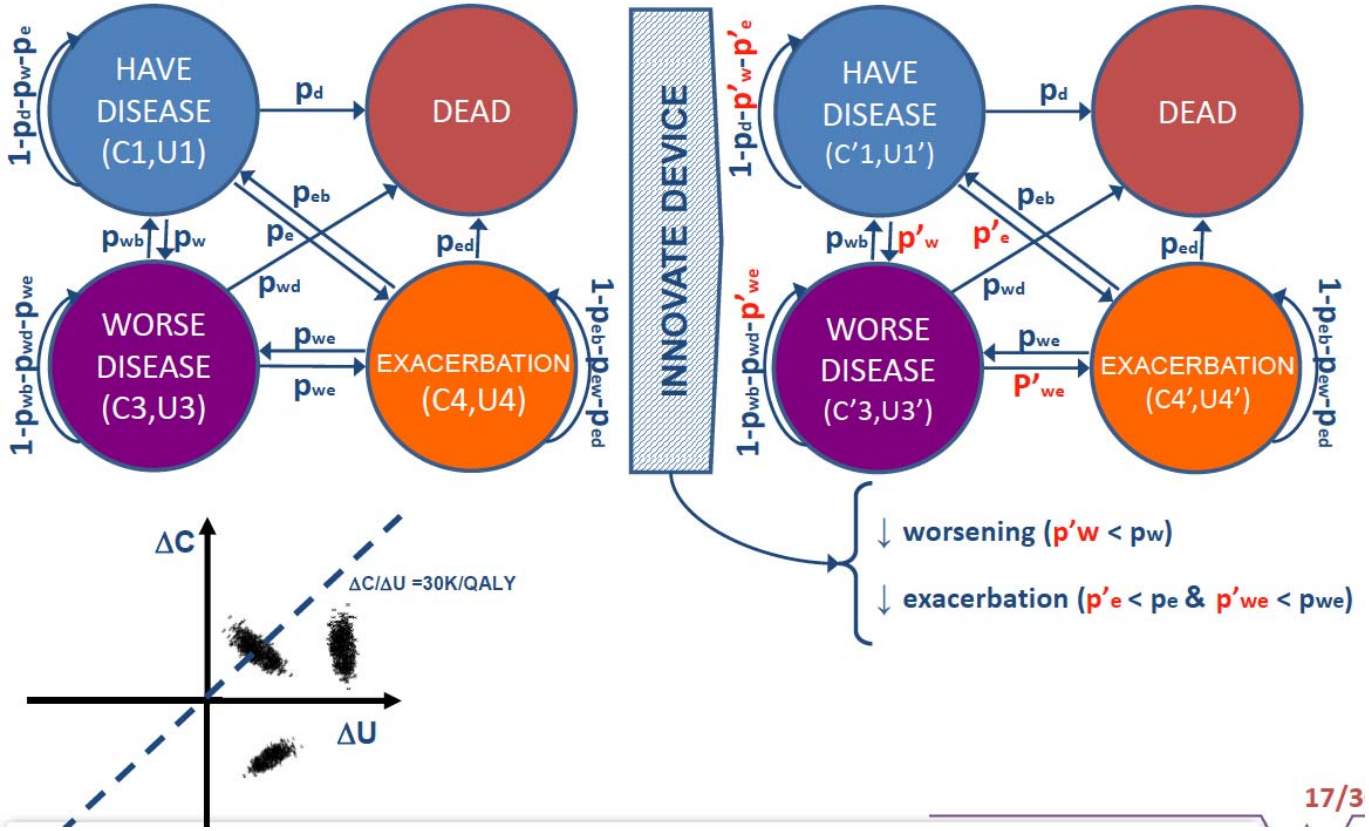
Confronto

Table 2. Characteristics of Markov Approaches

Feature	Monte Carlo	Markov Cohort	Fundamental Matrix
Transition probabilities	Time dependent	Time dependent	Constant
Incremental utilities	Time dependent	Time dependent	Constant
Accuracy	Cycle dependent	Cycle dependent	Invariant
Computation required	Most	Moderate	Least
CALCULATES			
Expected utility	Yes	Yes	Yes
Variability measures	Yes	No	Yes
Sensitivity analysis	Yes	Yes	Yes

e-HTA: Modelli di Markov

- Il modello di Markov viene applicato considerando la situazione attuale e i diversi costi, utilities e probabilità di transizione se il NUOVO DISPOSITIVO viene utilizzato
- La soluzione permette di collocare il punto del nuovo dispositivo sul diagramma dei C/U e di valutare, mediante l'incertezza, se il nuovo dispositivo ha "spazio" oppure no…



On line tool Markov chain

Markov Chain Simulation for Health Economics

http://www.nottingham.ac.uk/match/research/tools/markovtoolmain.html

This web-based tool allows the user to model the transition of a population of patients through a series of health states that are followed over time, which may include for example: living with a particular disease; having a treatment; being cured; having complications; or becoming deceased. These states are connected so that in any one time-step (typically using a cycle time of one year), there is a probability of a patient staying in their existing state or moving to a different one, and it is possible to move between specified health states in either direction. In this way it is possible to model either the progression of a chronic disease, which may includes worsening or improvement (such as the appearance or healing of a wound) or the consequences of treatment of an acute condition (such as surgery and its possible complications and follow-up). Cost and quality of life incurred in each cycle are added up incrementally as the model progresses.

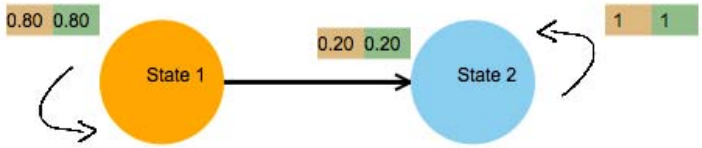
Tool features

- The number of states may be chosen between 2 and 5. These are shown on separate web-pages as bubble diagrams and can be navigated by clicking on the buttons above. States may be joined up graphically by mouse-clicking to add arrows in either direction between states.
- Transition probabilities between states are entered.
- Relevant data are entered for each state: the annual cost of being in the state, quality of life (measured as a utility between 0.00 and 1.00) in that state. In addition, in the first cycle a different cost or utility may be specified.
- The model can be run for a specified number of cycles (time step measure in years) and for a specified size of population.
- The model may be run either with a single set of data or as a comparison, where one model (Base case) is compared side by side with another (Innovation) with the same number of states, where any of the connections and their probabilities and state data (costs and/or utilities) may be different between the two models. This allows an innovation to be compared to the Base case (incumbent) technology.
- The model includes discounting, where the value of costs and utilities are reduced each year according to a fixed percentage, as the model proceeds into the future. A typical discounting percentage (as used by NICE) is 3.5% and so, in this case, a cost of £100 in year one is reduced to £100 divided by 1.035 in year two, by £100 divided by 1.035^2 in year three, and so on. Likewise a utility of 0.8 in year one is reduced to 0.8 divided by 1.035 in year two.
- The model may be solved in one of two ways: analytically using a Cohort method which provided a single answer, or run probabilistically using a Monte Carlo simulation method which provides a distribution of answers around a mean which is the same mean as the answer found in the Cohort method.

Tool outputs

- After the model (or pair of models) is run for a population of patients, for example 10,000 patients for 20 cycles, it is possible to see:
- Number of patients in each final state i.e. how the patient population is distributed amongst the states after the last cycle is completed. The results are shown graphically.
- Average patient benefit accrued, calculated from the utility in each year, expressed as Quality Adjusted Life Years (QALYs). In the case of the Monte Carlo simulation, the maximum and minimum QALY of the patient population is also found.
- Average cost per patient accrued over the time of the model, calculated by adding up the costs of each patient living in each health state. In the case of the Monte Carlo simulation, the maximum and minimum costs are also found.
- In the case of comparison of two models the Incremental Cost Effectiveness Ratio (ICER), the difference in costs divided by difference in QALYs, is calculated.

Esempio



Transition Matrix - Base Case		
	State 1	State 2
State 1	0.80	0.20
State 2	0	1

Transition Matrix - Innovation		
	State 1	State 2
State 1	0.80	0.20
State 2	0	1

Cost & Utilities - Base Case		
	State 1	State 2
Initial Cost	374	0
Incremental Cost	374	0
Initial Utility	0.81	0
Incremental Utility	0.81	0

Cost & Utilities - Innovation		
	State 1	State 2
Initial Cost	374	0
Incremental Cost	374	0
Initial Utility	0.81	0
Incremental Utility	0.81	0

Population: 1000 Cycles: 10 Discounting: 0.03

Start Cohort Analysis

Cost (Base Case): 1550.2767 Cost (Innovation): 1550.2767

QALYs (Base Case): 3.3576 QALYs (Innovation): 3.3576

ICER: N/A

Iterations: 5000 Cycles: 10 Discounting: 0.03

Start Monte Carlo Analysis

Cost (Base Case): 1542.8942 Cost (Innovation): 1558.2454

QALYs (Base Case): 3.3416 QALYs (Innovation): 3.3748

Minimum Cost (Base Case): 374 Minimum Cost(Innovation): 374

Maximum Cost (Base Case): 3484.4104 Maximum Cost (Innovation): 3484.4104

ICER: 462.3855

Riferimenti

La linea della lezione a alcuni lucidi sono stati presi dalla presentazione che dr ing Leandro Pecchia (Univ. of Warwick) ha svolto per la scuola COST su HTA svoltasi presso l'Ospedale Pediatrico Bambin Gesù ad Aprile 2016….