Decision Tree and Markov Model

2023年10月03日

Agenda

- Introduction of decision tree and Markov model
- Survival Analysis
- R/heemod

Part I: Decision tree and introduction of Markov Model

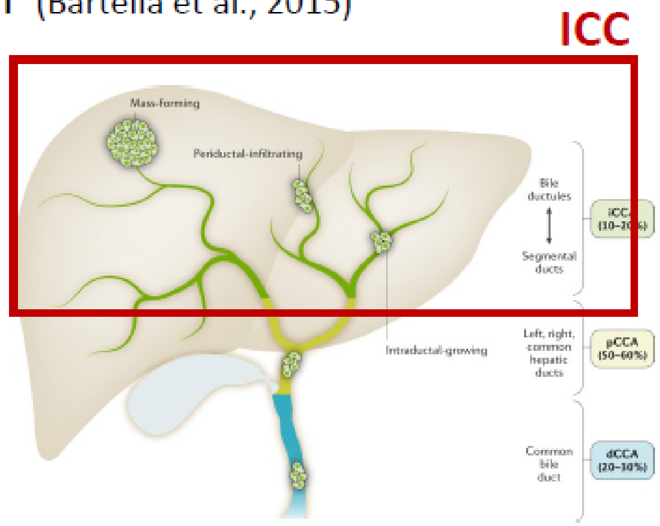
Wrap up:

- Specifying the decision problem
- structuring the decision model
- Output of CEA: ICER, CE plane, NHB, NMB

1-1. Research Background:
Introduction to Intrahepatic Cholangiocarcinoma

- Intrahepatic cholangiocarcinoma (肝內膽管癌; ICC), a subtype of cholangiocarcinoma (膽管癌; CCA), occurs in the endothelial cells of bile ducts within the liver (Bartella et al., 2015)

- ICC is a rare cancer and has a poor prognosis (Taiwan Cancer Registration, 2022)
  - ➢ Incidence (Taiwan): **3.3** per 100,000 people; **1336** cases in 2019
  - ➢ Prognosis (Taiwan): 5-year survival **<20%** (Dr. Chiang, 2021)



(Banales et al., 2020)

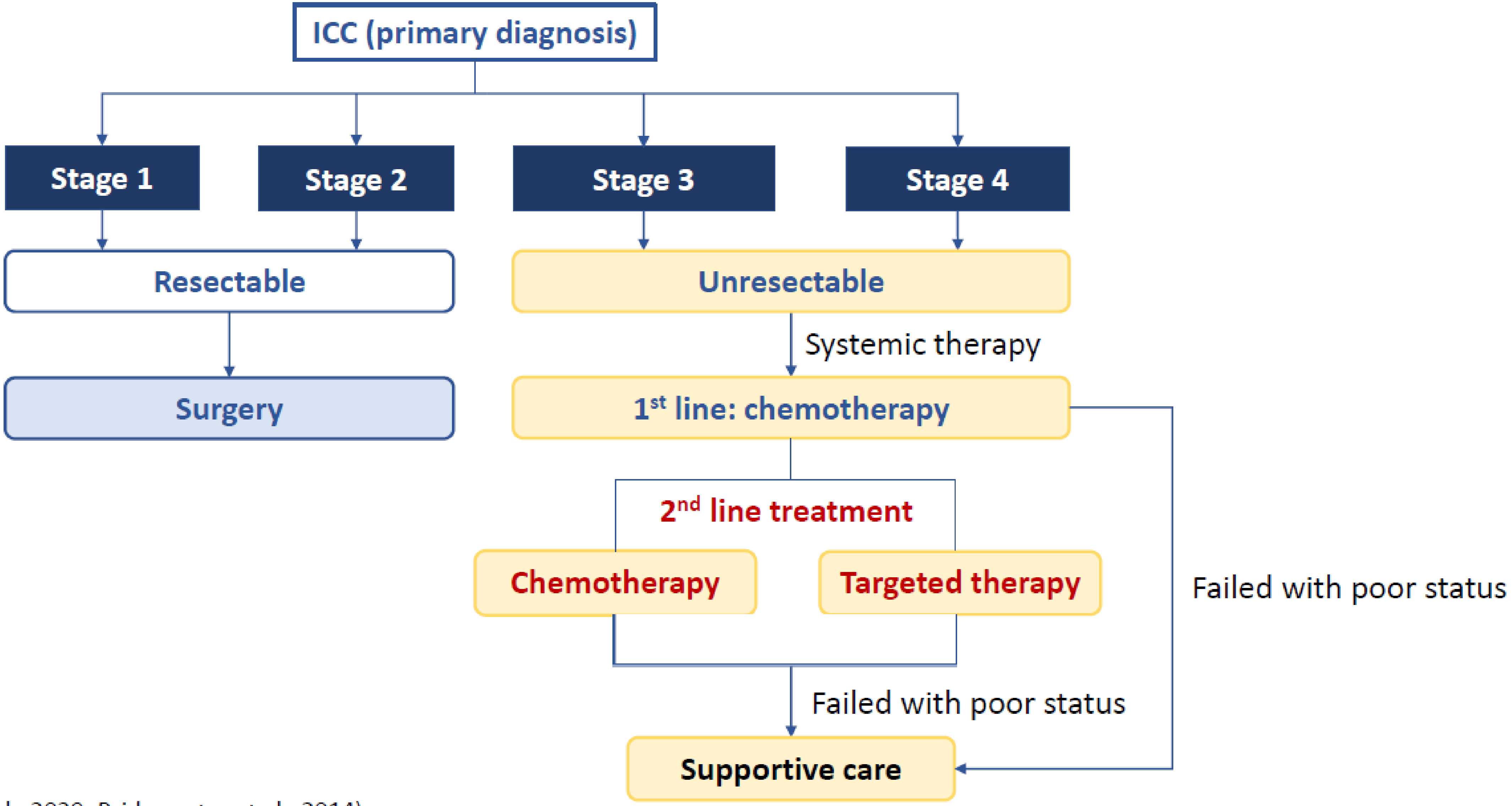
- Staging (AJCC TNM staging system)

AJCC: American Joint Committee on Cancer
TNM: Tumor, Nodes, Metastases

Stage 1 →	**Stage 2** →	**Stage 3** →	**Stage 4**
single tumor; without vascular invasion	>1 tumors; with/without vascular invasion	tumor(s) has spread to nearby tissue/organ/ lymph nodes	tumor(s) with distant metastasis

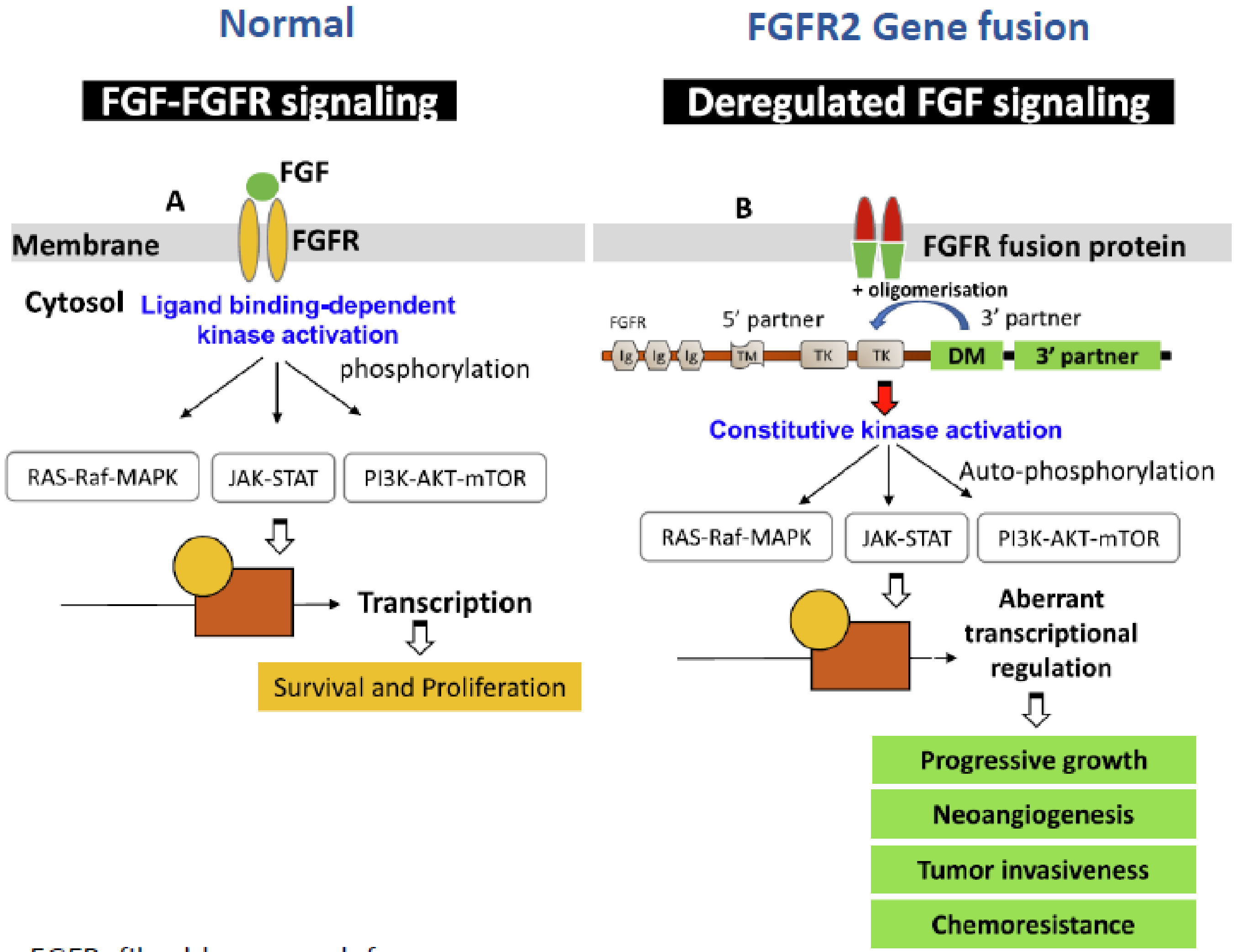
- ICC is asymptomatic in the early stages → **70%** ICC are diagnosed at **advanced stages** (Banales et al., 2020)

1-1. Research Background:
Treatment of Intrahepatic Cholangiocarcinoma



(Banales et al., 2020; Bridgewater et al., 2014)

1-1. Research Background:
Treatment of Intrahepatic Cholangiocarcinoma–Targeted Therapy



- **Targeted therapy**
  - Specific gene mutations that lead to abnormal growth of tumor cells, such as *FGFR2* gene fusion, have been identified
  - **FGFR2 kinase inhibitor**

    Block the deregulated signal pathway → Tumor cell growth is inhibited
  - **Genetic testing**

    Used to identify patients with *FGFR2* gene fusion
  - **Pemigatinib**

    U.S. FDA approved (April, 2020)

(Goyal et al., 2021; Rizzo, 2021; Ronnekleiv-Kelly et al., 2020)

FGFR: fibroblast growth factor receptor
FGF: fibroblast growth factor;
FDA: U.S. Food and Drug Administration

1-1. Research Background:
Treatment of Intrahepatic Cholangiocarcinoma–Systemic Therapy

- **International guidelines vs. Taiwan's reimbursement policy**

	1st line	2nd line
International guidelines: NCCN/ESMO (Benson, et al., 2021; ESMO,2019; NICE, 2021)	Chemotherapy • **Gemcitabine + Cisplatin** • Others (gemcitabine-based regimens)	Chemotherapy • **Modified FOLFOX (mFOLFOX)** (Folinic acid+5FU+Oxaliplatin) • Others Targeted therapy • **Pemigatinib** (*FGFR2* gene fusion: +)
Taiwan (中央健康保險署, 2021)	Chemotherapy • **Gemcitabine + Cisplatin** • Others (gemcitabine-based regimens)	Chemotherapy • 5FU • Cisplatin • Gemcitabine • Combination of above drugs

Taiwan

- **mFOLFOX**
  TFDA: **NOT** approve oxaliplatin
  (NHI: not reimbursed)
- **Pemigatinib**
  TFDA: approve
  NHI: **NOT** reimbursed

5FU: 5-fluorouracil; ESMO: European Society for Medical Oncology; NICE: National Institute for Health and Care Excellence; NHI: National Health Institution, Taiwan; TFDA: Food and Drug Administration, Taiwan

1-1. Research Background:
Drug Costs of the 2nd Line Systemic Therapy

- **Cost of 2nd line systemic therapy** Body surface area (BSA) = 1.6 m^2

▶ International new treatment regimen

mFOLFOX

Dosing (per 2 weeks)
- Folinic acid (leucovorin): 175 mg
- 5FU: 400 mg/m^2 bolus ; 2400 mg/m^2
- Oxaliplatin: 85 mg/m^2

→ **Estimated cost: NT$6,000 per 2 weeks**

(Costs calculated from NHI drug reimbursement price)

Pemigatinib

Dosing (per 3 weeks)
- Pemigatinib: 13.5 mg once daily

→ **Import price: NT$200,000 per 3 weeks**

(Cost from market enquiry)

▶ Taiwan's current treatment regimen

5FU

Dosing (per 2 weeks)
- 5FU: 2400 mg/m^2
- Folinic acid (leucovorin): 400 mg/m^2

→ **Estimated cost: NT$1,000 per 2 weeks**

(Costs calculated from NHI drug reimbursement price)

mFOLFOX NT$3,000/week

pemigatinib NT$66,666/week

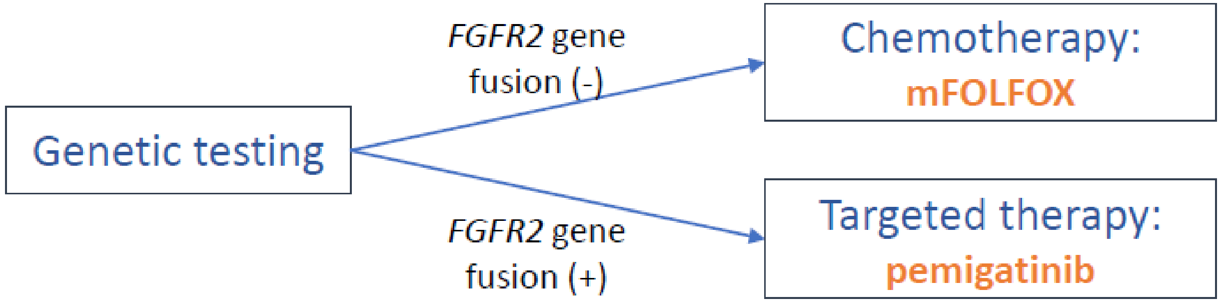
130x

6x

5FU NT$500/week

1-2. Motivation and Knowledge Gap

- **Second line treatment regimens for advanced ICC**
  - **International new treatment regimen**
    - FGFR2 (-): mFOLFOX
    - FGFR2 (+): pemigatinib
  - **Taiwan current treatment regimen**
    - **5FU** (the most common prescription pattern in NHI reimbursement policy)
  - **Efficacy: International new treatment regimen** > Taiwan current treatment regimen
  - **Drug cost: International new treatment regimen** > Taiwan current treatment regimen

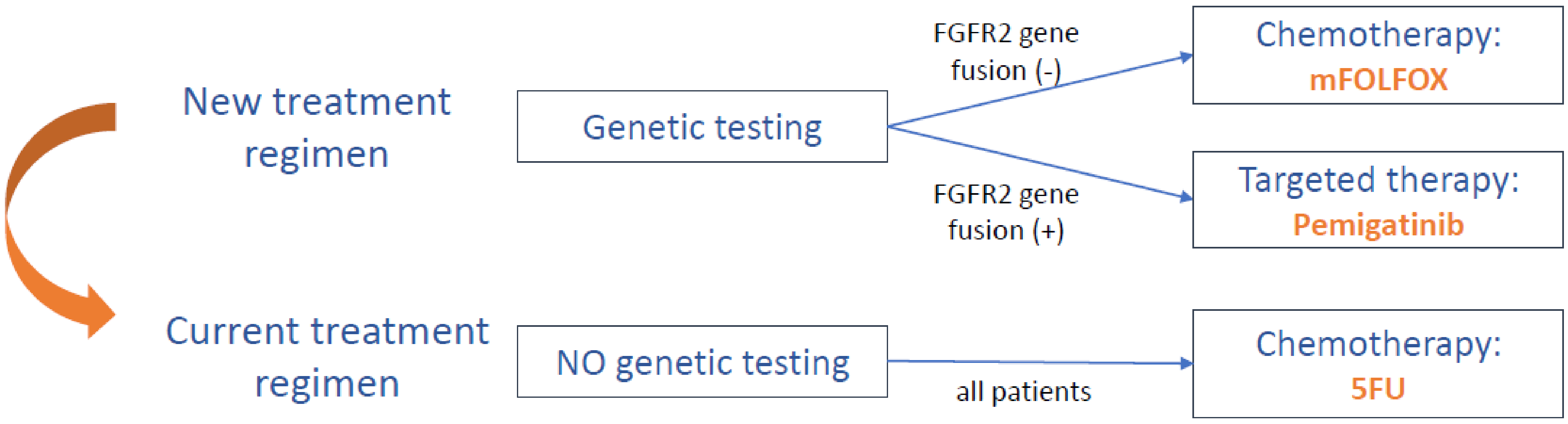


Medical technology gap: Taiwan NHI has not reimbursed mFOLFOX and pemigatinib

Knowledge gap: No local CEA evidence for the new treatment regimen

1-3. Research Objective and Research Question

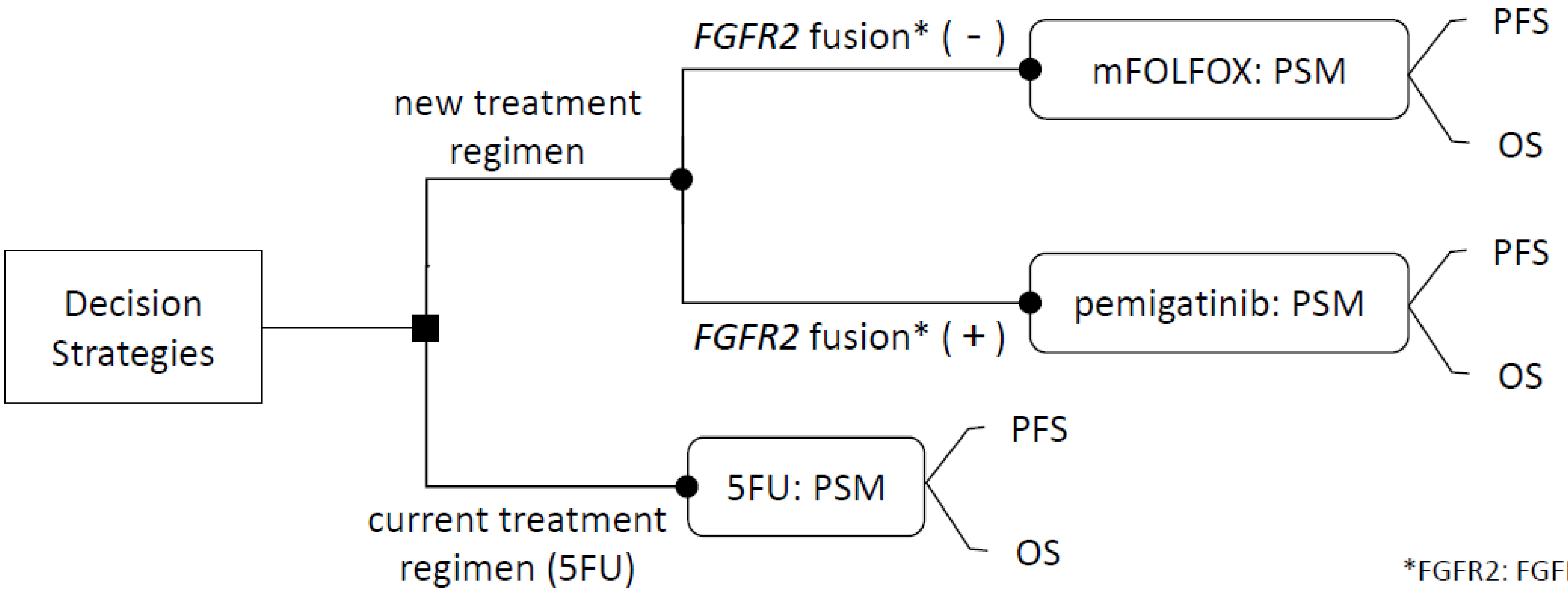
- **Research objective**
  - ➢ To evaluate the cost-effectiveness of the **2nd line** **new treatment regimen** for advanced ICC patients.
  - ➢ To find the cost-effective pricing of pemigatinib.



- **Research question**
  - ➢ From the Taiwanese NHI payer's perspective, is the **2nd line** **new treatment regimen** cost-effective compared with the **current treatment regimen** for advanced ICC patients?
  - ➢ Which pricing is cost-effective for the 2nd line new treatment regimen?

3-1. Study Design

- **Target population:** advanced ICC patients who failed their 1st line treatment
- **Treatment regimens:** 2nd line treatment for advanced ICC patients
  - ➢ Intervention: new treatment regimen (mFOLFOX and pemigatinib)
  - ➢ Comparator: current treatment regimen (5FU)



*FGFR2: FGFR2 gene fusion/rearrangement

This study is approved by the Institutional Review Board of National Yang Ming Chiao Tung University (YM111012E).

3-2. Building the Decision Analytical Model

- **Decision analytical model**
  - Partitioned survival analysis (PartSA) model
- **Model structure**
  - 3 Health states
    1. **Progression free (PF)**
       - Clinical performance: stable
       - Treatment: 2nd line new or current regimen
    2. **Progressed disease (PD)**
       - Clinical performance: tumor progressed
       - Treatment: supportive care
    3. **Death**
  - Cycle length: 1 month
  - Time horizon: 5 years
  - Discounting rate: 3% (CDE, 2014)
- **Perspective**
  - National Health Insurance Administration, Taiwan
- **Outcomes**
  - Life years, quality-adjusted life years (QALYs), direct medical costs, cost-effectiveness results
- **Parameters**
  - Proportion of ICC patients with FGFR2 gene fusion
    - Taiwan: 7.7% (Chiang et al., 2021)
  - Willingness-to-pay (WTP, λ) = 3 times GDP per capita
  - Clinical efficacy
  - Utility
  - Direct medical costs

3-4. Cost-effectiveness Analysis: Base-Case Analysis

Software: TreeAge Pro 2021

- **Incremental cost effectiveness ratio (ICER)**

  The cost per unit of the health outcome/effect.

  Function: $\boxed{\mathrm{ICER} = \frac{C_2 - C_1}{E_2 - E_1} = \frac{\Delta C}{\Delta E}}$

- **Net monetary benefit (NMB)**

  Function: $\boxed{\mathrm{NMB} = \lambda \times \Delta E - \Delta C}$

C_1 : the cost under the comparator.
C_2 : the cost under the intervention of interest.
E_1 : the effectiveness under the comparator.
E_2 : the effectiveness under the intervention of interest.
λ : threshold, willingness to pay (WTP)

✓ **Decision criteria**

- ICER < λ
- NMB > 0

λ = 3 times of GDP per capita in Taiwan (2021)

(Edlin et al., 2015; Gray et al., 2010)

4-2. Base Case Analysis

- **Base-case: Cost-effectiveness outcomes in 5 years**

	Current regimen (5FU)	New regimen (mFOLFOX/pemigatinib)	Incremental change
Cost	524,472	984,168	459,697
Total cost of PF state	369,229	795,614	
• Genetic test cost	0	30,000	
• Medication costs (PF)	63,430	387,176	
• Non-medication cost (PF)	305,799	378,437	
Total cost of PD state	155,243	188,555	
Life years			
Progression-free	0.36	0.48	0.12
Overall	0.67	0.86	0.19
Quality-adjusted life years			
Progression-free	0.26	0.35	0.09
Overall	0.47	0.61	0.13
Incremental cost per QALY (ICER)		WTP (λ) = 3 times GDP (NT$2,889,684)	3,411,098
NMB			-70,269

LYs: life years, QALYs: quality-adjusted life years, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit

Findings:

- ICER (NT$ 3,411,098) > WTP (NT$2,889,684)
- NMB (NT$ -70,269) < 0

NOT cost-effectiveness in base-case analysis!

PSA results: CE cloud/CEAC

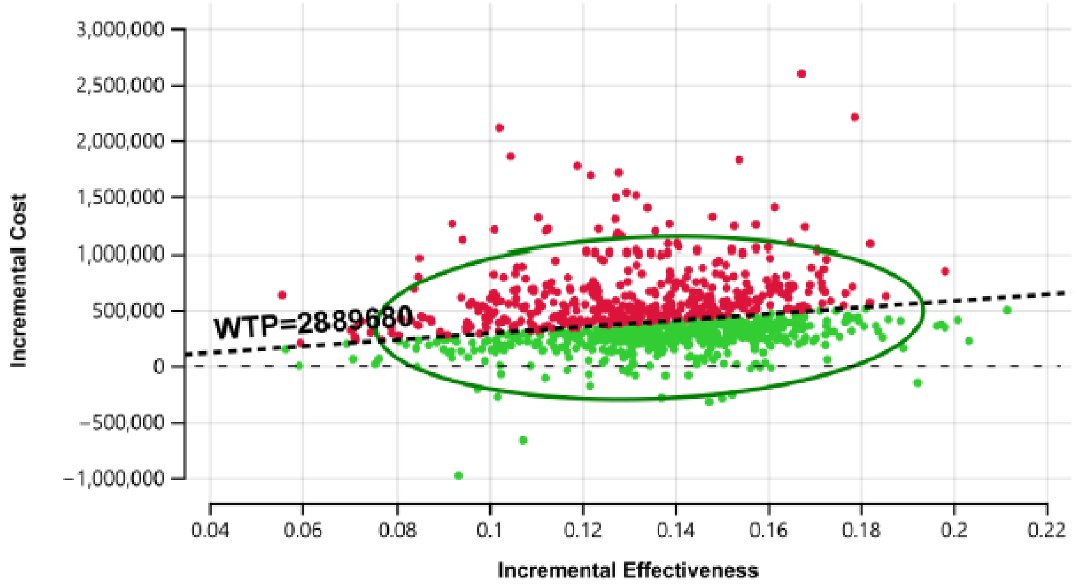


Figure 3. Cost-effectiveness cloud

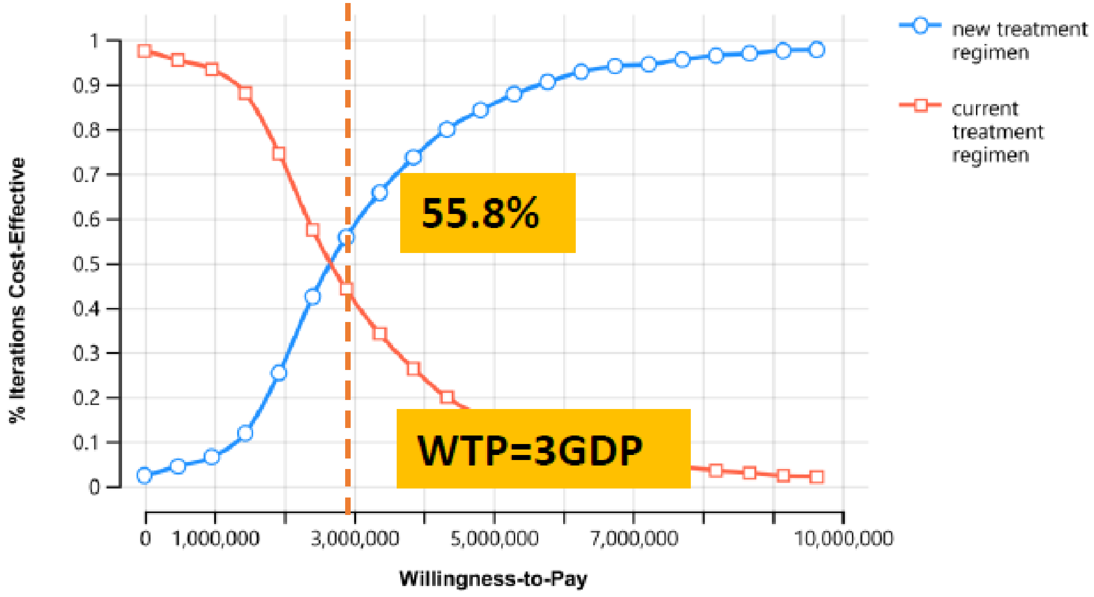


Figure 4. Cost-effectiveness acceptability curve (CEAC)

表六、第一年（晚期肝內膽管癌）研究設計

目標族群（Population, P）	第一線治療失敗的晚期肝內膽管癌患者 （模擬：1,000 人病患世代）
介入方案（Intervention, I）	晚期肝內膽管癌第二線新型治療方案：根據基因檢測結果 • →FGFR2 陽性：pemigatinib • →FGFR2 陰性：FOLFOX
對照方案（Comparator, C）	晚期肝內管癌第二線現行治療方案： 健保給付之傳統化療藥品（以 5FU 為例）
結果（Outcome, O）	存活年、醫療成本（健保給付）
經濟模式	分段存活模型（partitioned survival model, PartSM）
疾病模式	分為無疾病惡化（progression free, PF）、疾病惡化（progressed disease, PD）以及死亡（death）
週期（Cycle）	
追蹤期間（Time horizon）	
折現率	
成本效益閾值（λ）	三倍的臺灣人均國內生產毛額（Gross Domestic Product, GDP）
分析估計	ICER、NHB、NMB 敏感度分析：EVPI、EVPPI
情境分析	依據不同的價格（price of pemigatinib）與外推存活曲線（extrapolated survival curve）分別進行情境分析

Principle of efficiency: incremental cost over incremental consequence

- cost-effectiveness analysis denotes an economic evaluation that measures costs in a monetary unit and quantifies a single consequence in a physical or natural unit (e.g., the number of successfully treated patients, the number of life years gained, the number of symptom days averted).

$$\text{Incremental cost-effectiveness ratio} = (C_1 - C_0) / (E_1 - E_0)$$

- C1 is the cost of the health technology;
- C0 is the cost of the comparator technology;
- E1 and E0 are the consequences of the technology and the comparator, respectively.

Review of Basics

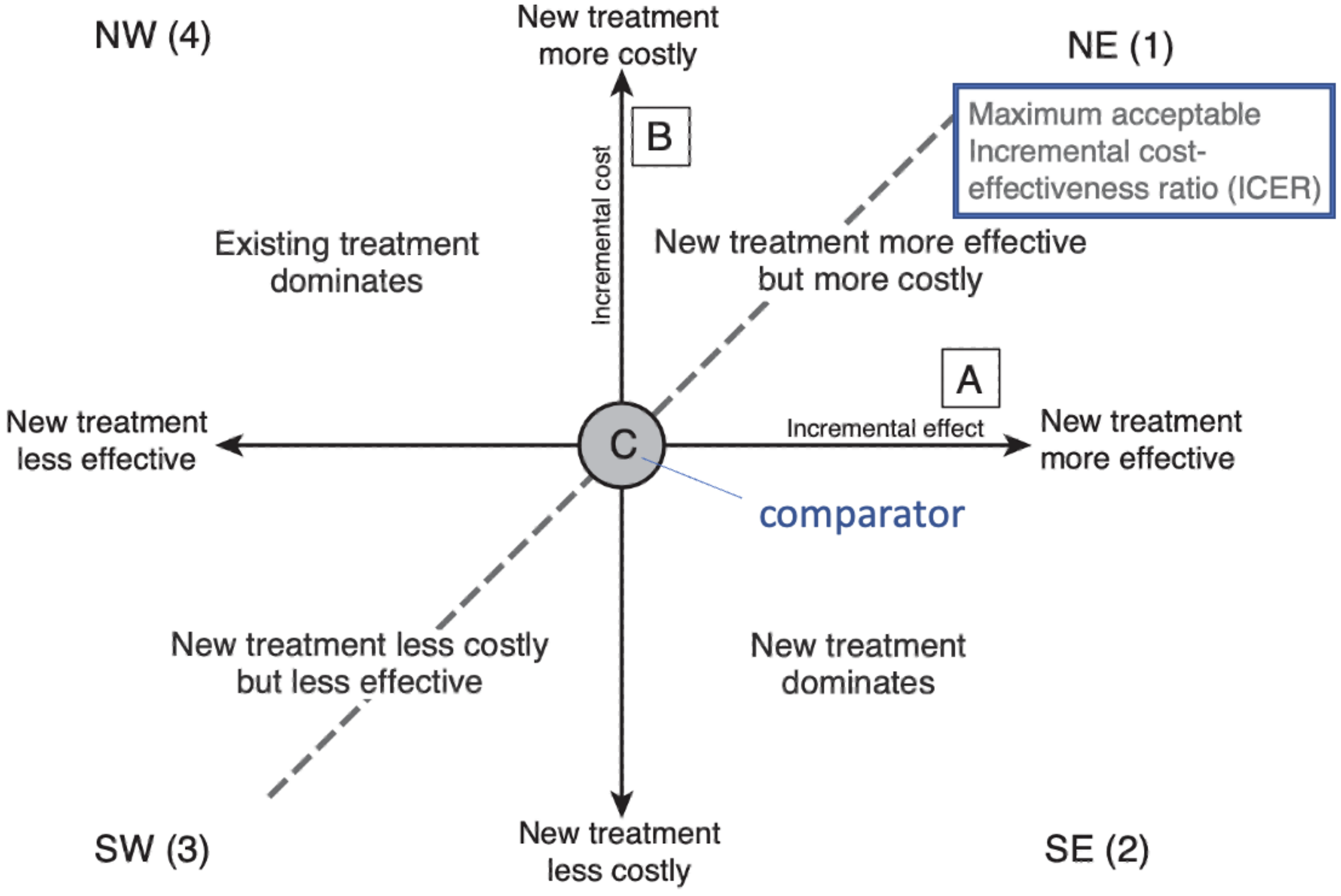
Threshold value

(willingness to pay)

- How much the decision-maker is willing to pay for health gain

= the maximum value of λ

Cost-effectiveness plane:



Net health benefit/Net monetary benefit

- **Net monetary benefit (NMB)** is a summary statistic that represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit (for example a measure of health outcome or QALY) is known.

$$NMB: \quad \lambda \cdot \Delta E - \Delta C$$

- **Net health benefit (NHB)** is a summary statistic that represents the impact on population health of introducing a new intervention

$$NHB: \quad \Delta E - \frac{\Delta C}{\lambda}$$

Method

Trial-based vs. Analytical decision modeling

When to use

BMJ 2011;342:d1766

- Randomised trials do not always provide a sufficient basis for economic evaluations used to inform regulatory and reimbursement decisions
- Decision analytical modelling compares the expected costs and consequences of decision options by synthesising information from multiple sources and applying mathematical techniques, usually with computer software.
- The aim is to provide decision makers with the best available evidence to reach a decision

Types of economic evaluation

- Trial-based economic evaluation vs. model-based economic evaluation
- Decision-analytical modeling (approaches):
  - Decision tree
  - State Transition Model

Trial-based economic evaluation

- York Materials

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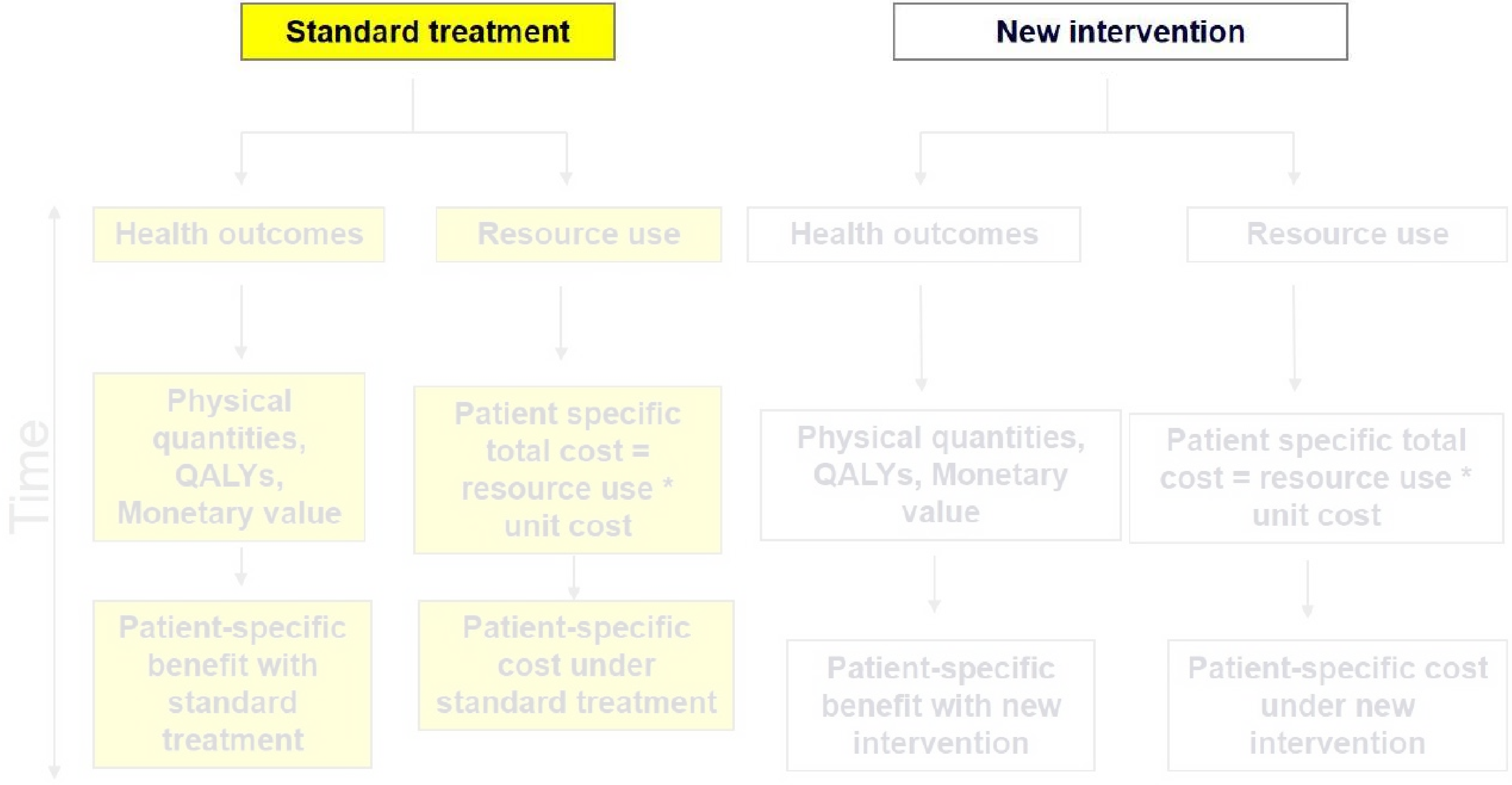
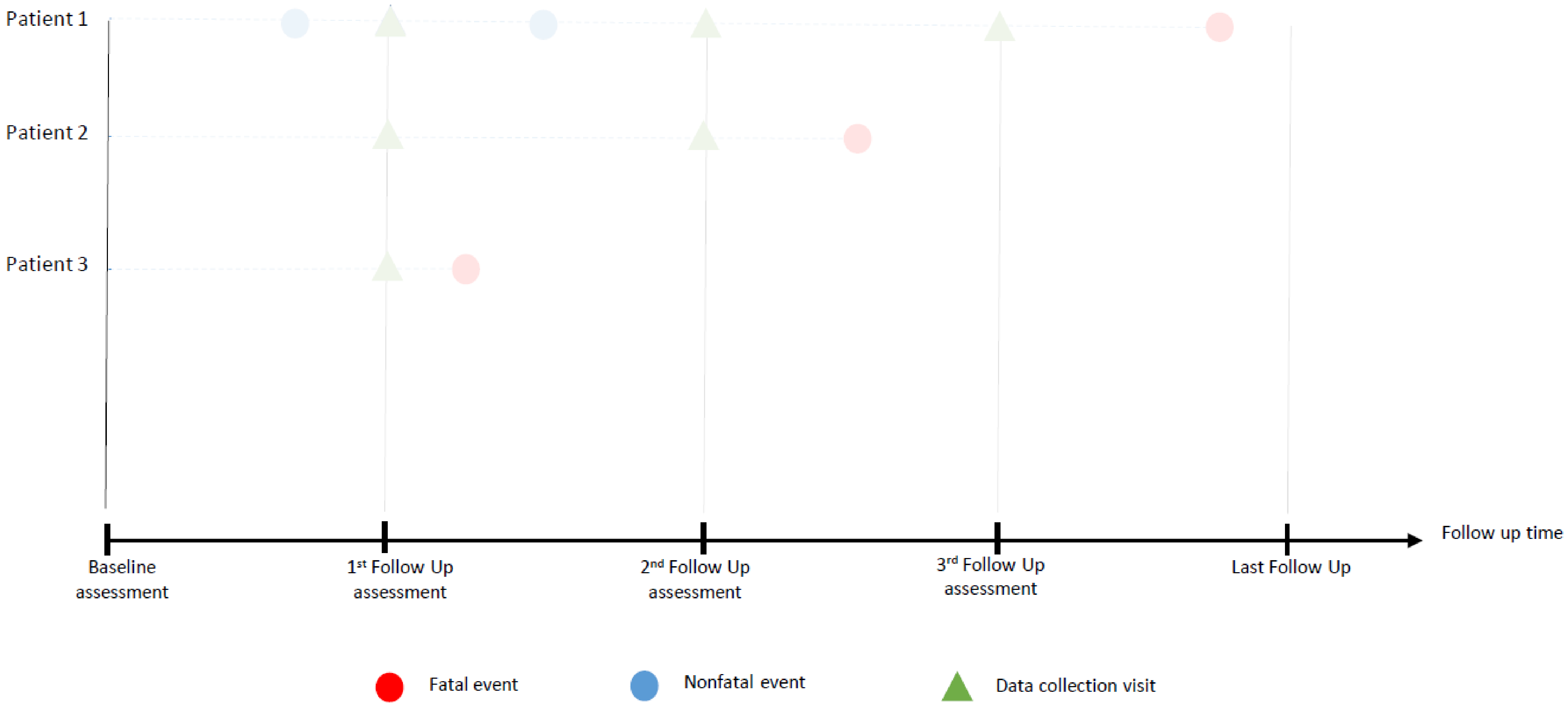
Structure of a RCT-based CEA



Patient's history and data accrual

(simple case with no censoring)



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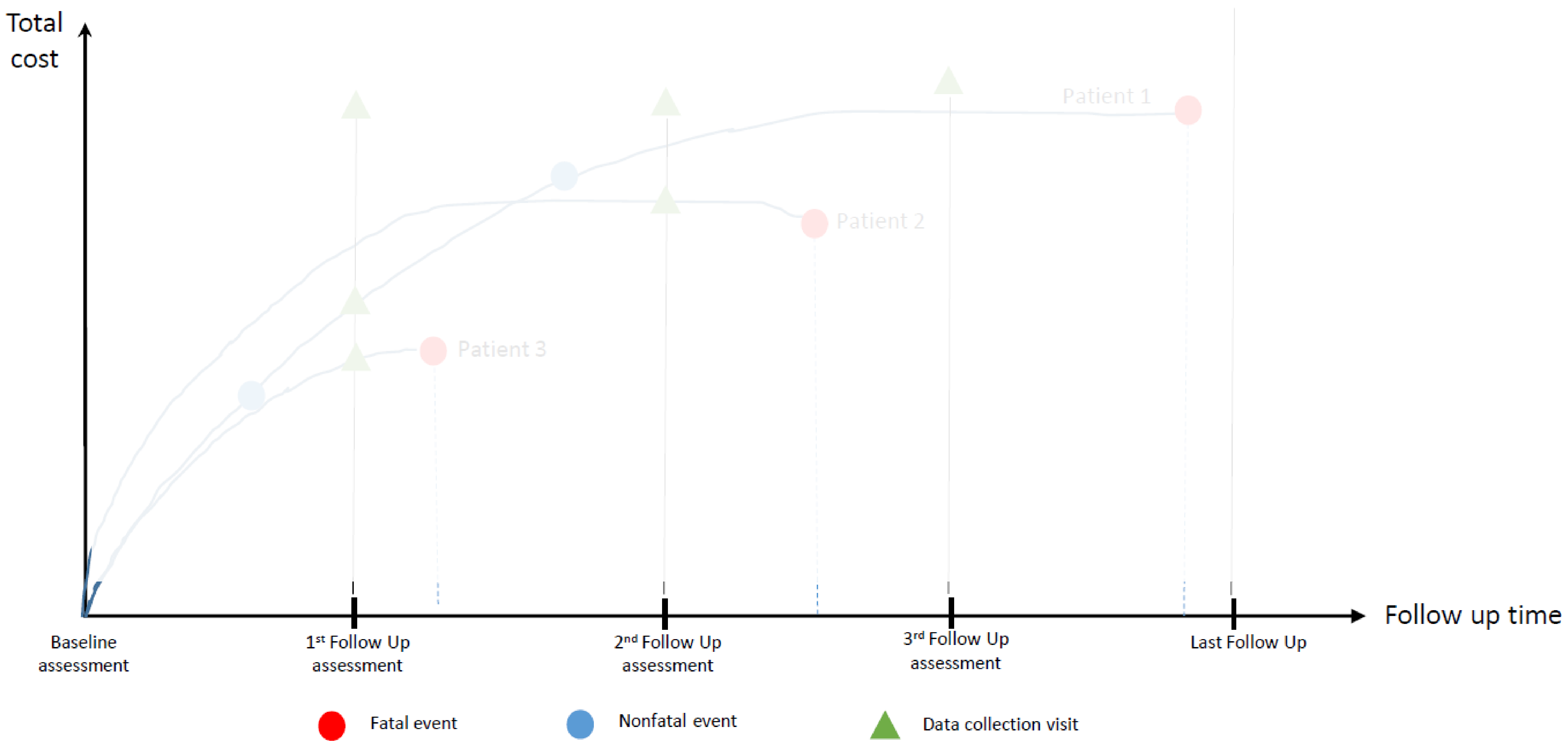


Patient’s history and data accrual

(simple case with no censoring)

Sample dataset

id	group	Follow up visit	EQ-5D	GP visits	Out-patient visits	In-patient LOS (days)	Medication use (mg)	Dead
1	0	0	0.80	NA	NA	NA	NA	0
1	0	1	0.85	2	1	0	180	0
1	0	2	0.87	3	1	2	180	0
1	0	3	0.54	0	3	20	340	0
1	0	4	-	-	-	-	-	1
2	1	0	0.80	NA	NA	NA	NA	0
2	1	1	0.83	2	1	3	160	0
2	1	2	0.60	4	1	15	180	0
2	1	3	-	-	-	-	-	1
2	0	4	-	-	-	-	-	1

Data structure

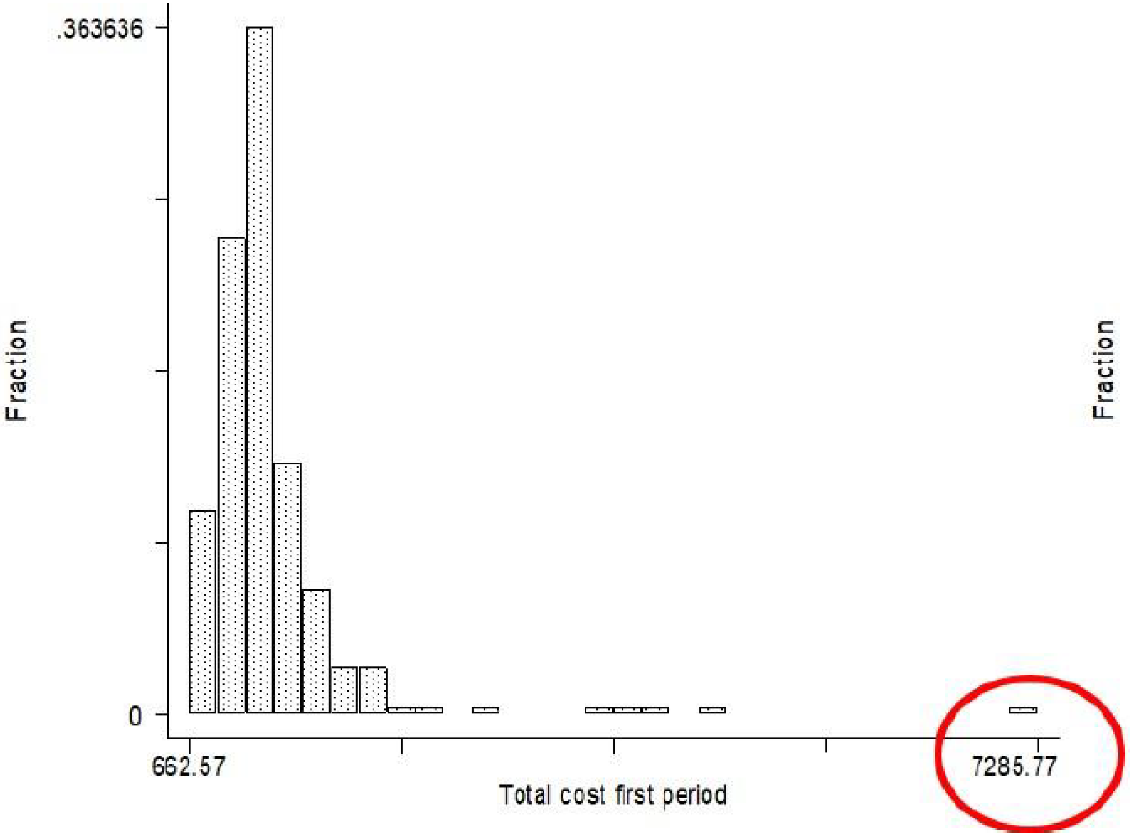
Two independent groups

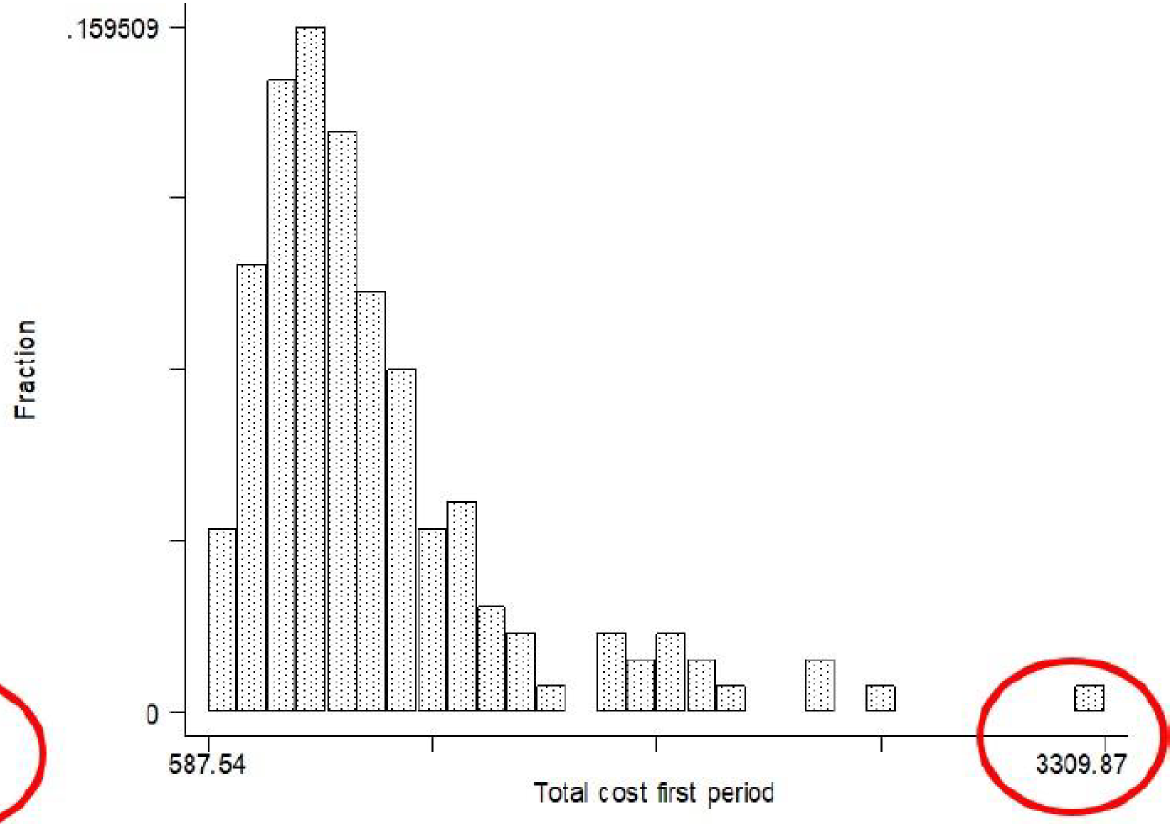
Control		Intervention	
Patient	(Cost, Effect)	Patient	(Cost, Effect)
1	C_c^1, E_c^1	1	C_n^1, E_n^1
2	C_c^2, E_c^2	2	C_n^2, E_n^2
3	C_c^3, E_c^3	3	C_n^3, E_n^3
.		.	
.		.	
n_c	C_c^n, E_c^n	n_n	C_n^n, E_n^n

Analysis of cost data

EVALUATE trial

	Abdominal	Laparoscopic
Cost (6 weeks)		
mean (SD)	1,286 (611)	1,561 (1,107)
median	1,167	1,290
range	(662 – 7,286)	(587 – 3,309)

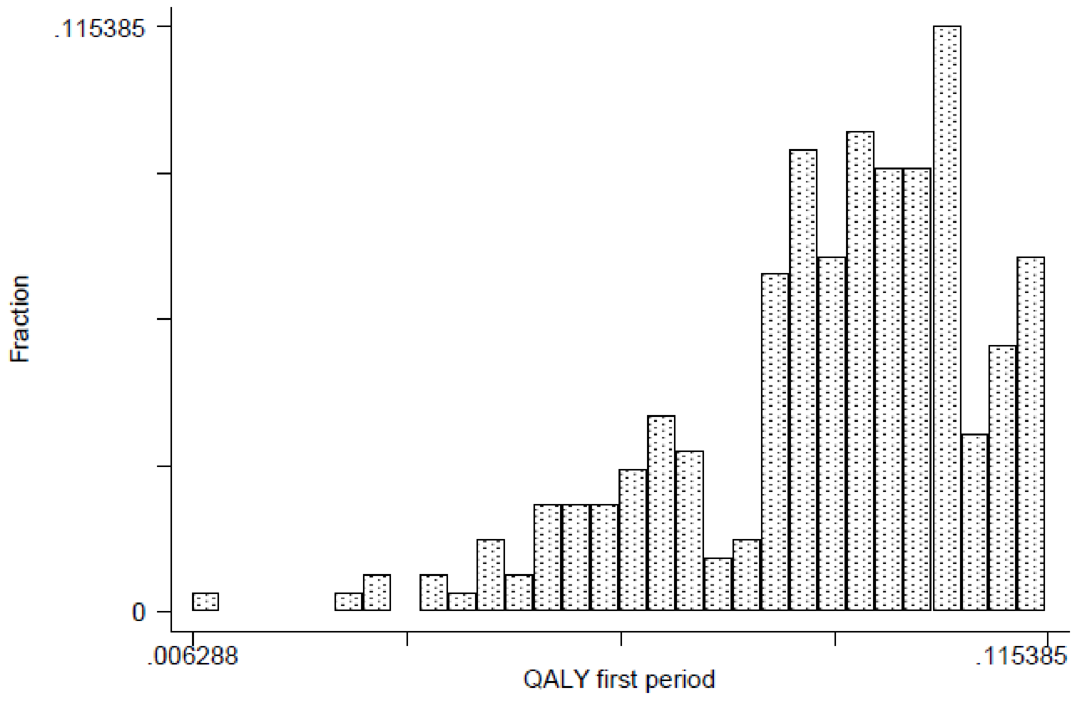


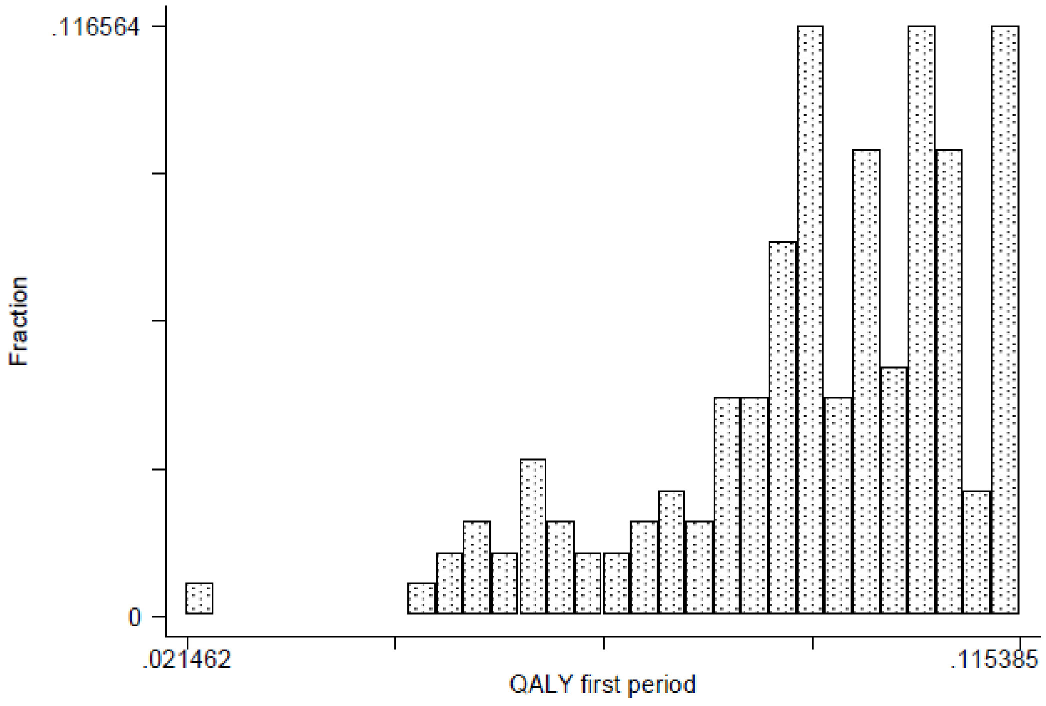


Analysis of effectiveness data

EVALUATE trial

	Abdominal	Laparoscopic
QALYs (6 weeks)		
mean (SD)	0.088 (0.019)	0.090 (0.020)
median	0.09	0.09
range	(0.006 - 0.115)	(0.02 - 0.115)

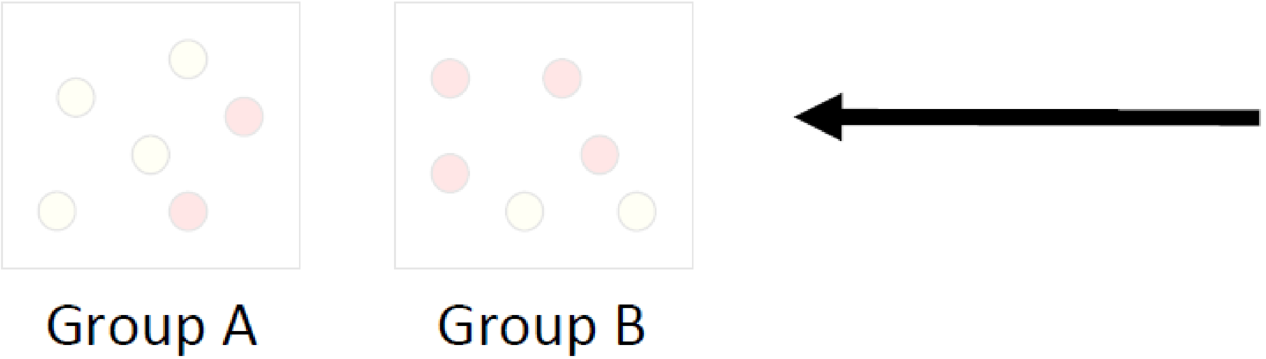




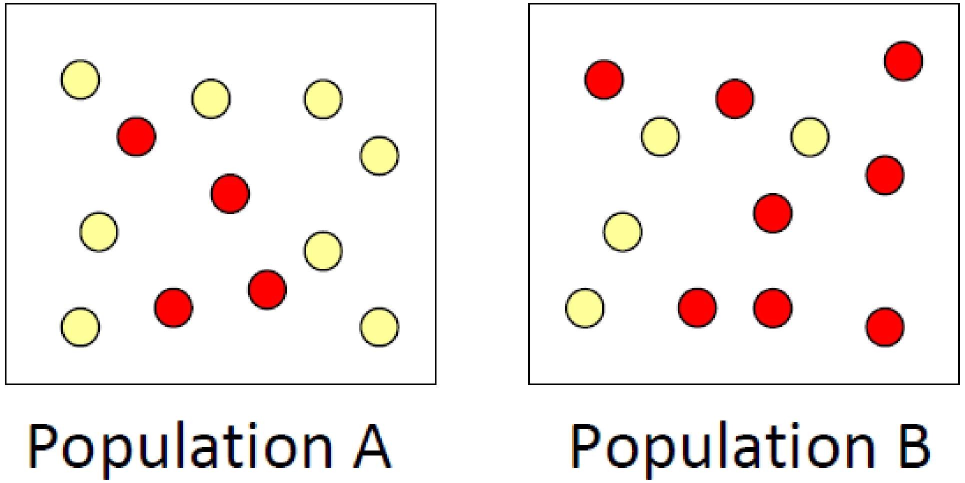
Quantities of interest

- The analysis of IPD is inherently stochastic; we need to estimate
  - Difference in mean costs: $\overline{\Delta C}$ = $(\overline{C_i} - \overline{C_c})$
  - Difference in mean QALYs: $\overline{\Delta E}$ = $(\overline{E_i} - \overline{E_c})$
  - Standard error of the mean costs: SE($\overline{\Delta C}$)
  - Standard error of the mean costs: SE($\overline{\Delta E}$)
  - Correlation coefficient between $\overline{\Delta C}$ and $\overline{\Delta E}$

Bootstrap method



Representative sample of the population, i.e. our trial sample



The objective is to analyse the sample data in order to be able to make some sort of statement about the population from which the sample was drawn

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Bootstrap for CIs

Observations from the sample	
1	C_c^1, E_c^1
2	C_c^2, E_c^2
3	C_c^3, E_c^3
..	
n_c	C_c^n, E_c^n
1	C_n^1, E_n^1
2	C_n^2, E_n^2
3	C_n^3, E_n^3
.	
n_n	C_n^n, E_n^n

1. Re-sampling with replacement N groups of equal size to the intervention and calculate the mean
2. Re-sampling with replacement N groups of equal size to the control and calculate the mean
3. Calculate difference between the two mean for each iteration
4. Use these data to calculate the CI for the ICER

Statistic from re-sampling	
1st	$\Delta C_c^1, \Delta E_c^1$
2nd	$\Delta C_c^2, \Delta E_c^2$
3rd	$\Delta C_c^3, \Delta E_c^3$
4th	$\Delta C_c^4, \Delta E_c^4$
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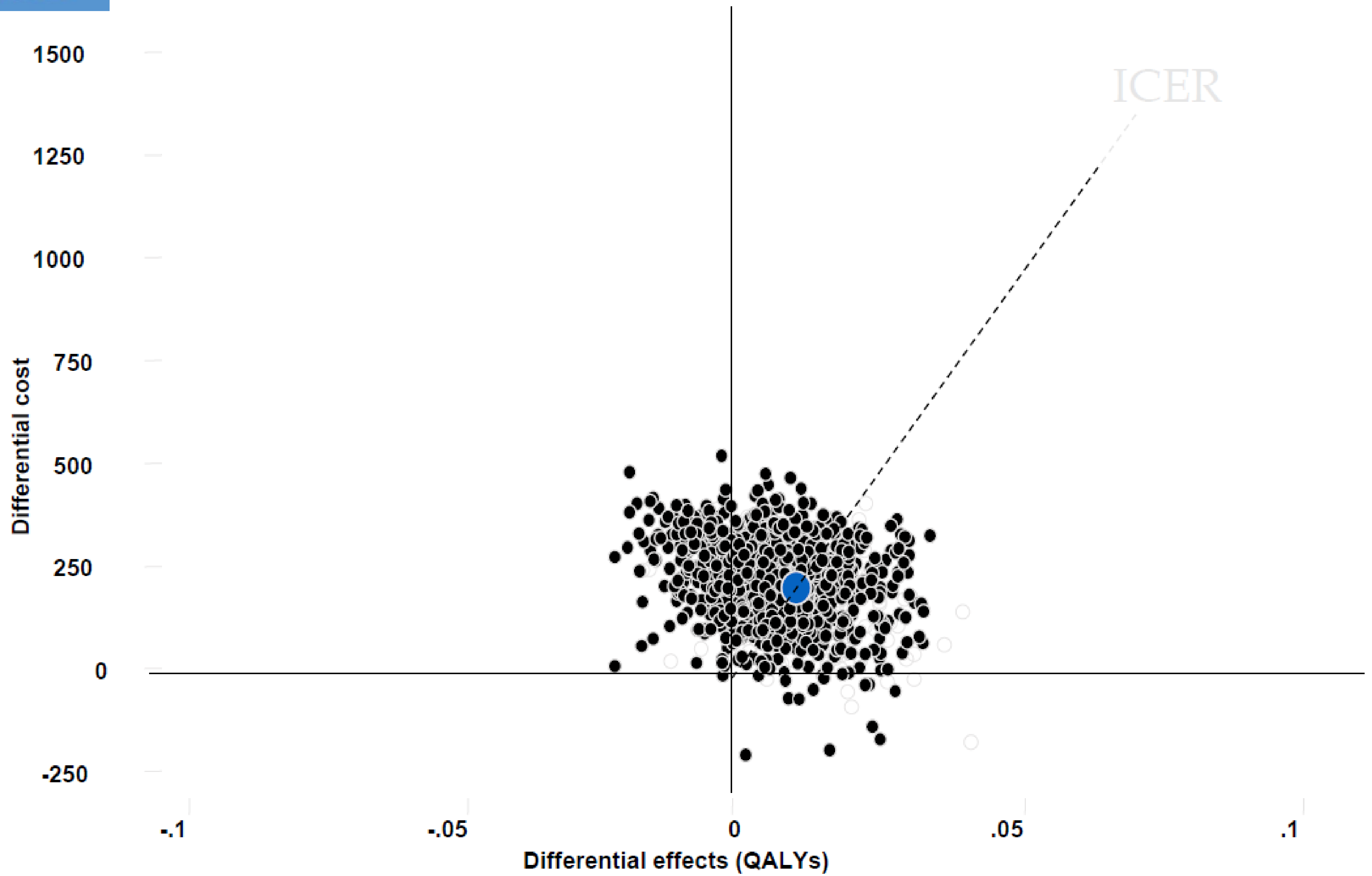
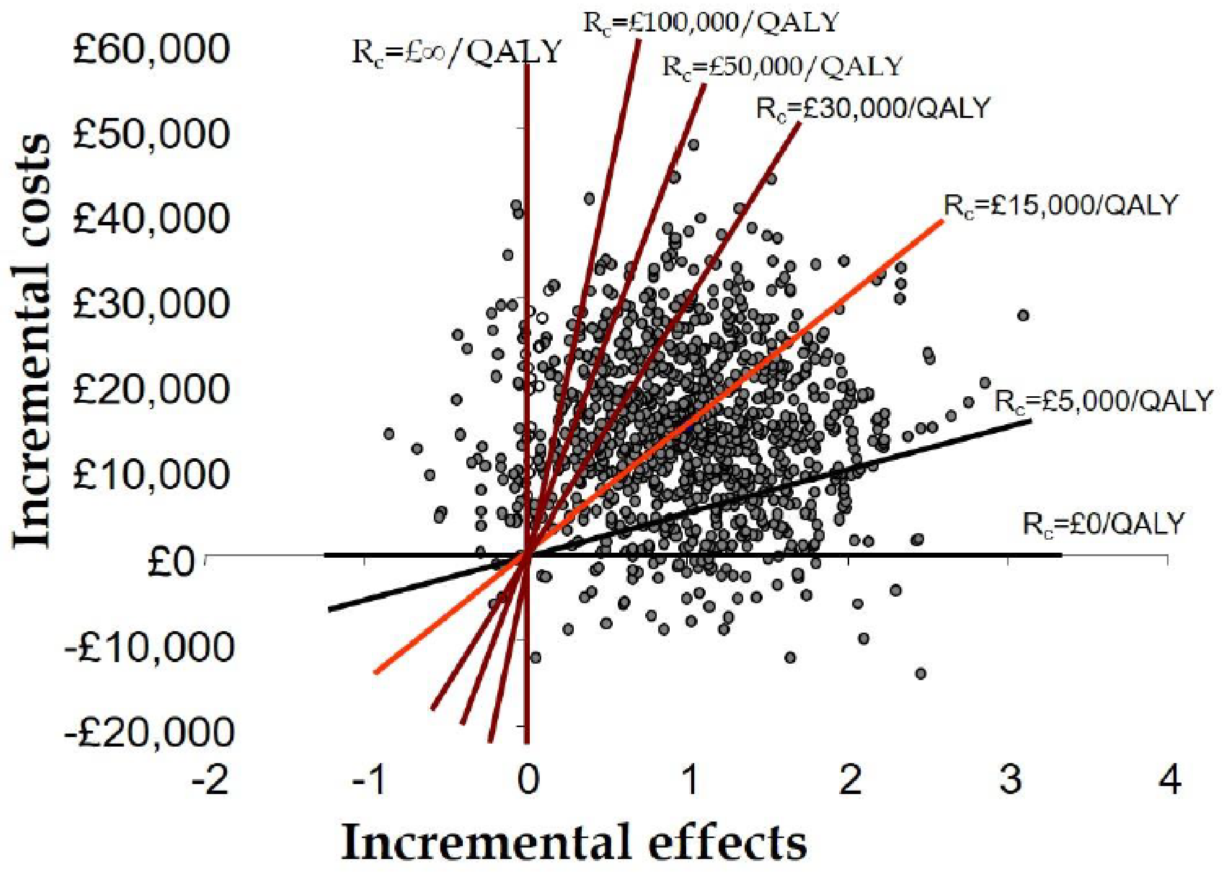
nth	$\Delta C_c^{th}, \Delta E_c^{th}$

Non-parametric bootstrap on the CE plane

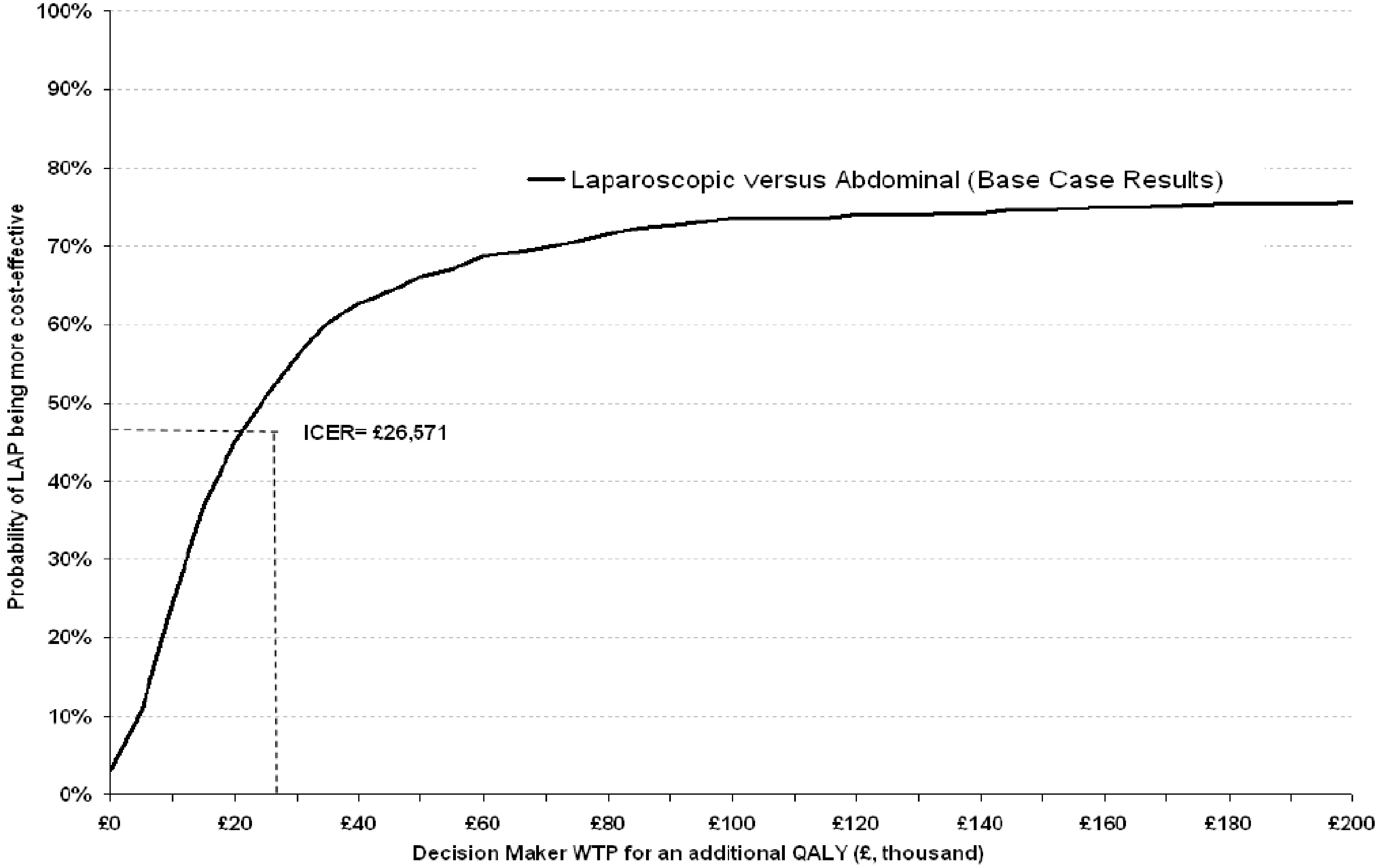


Building the CEAC



Source: Briggs (2001)

CEACs in the EVALUATE trial



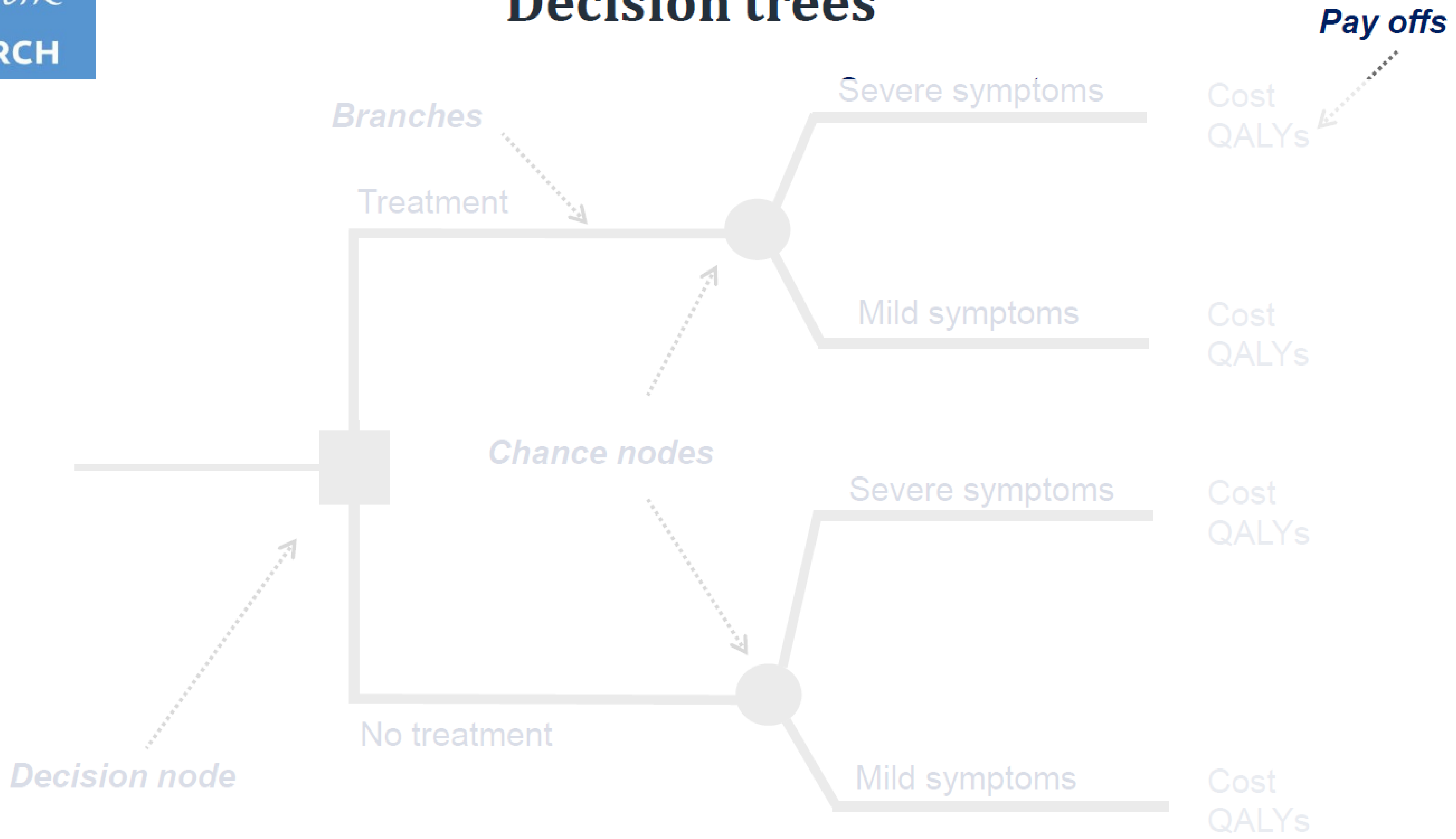
Source: Sculpher MJ, Manca A, *et al.* (2004)

Decision Analytic Modeling (Briggs)

- Cohort Models: a cohort model is any model which estimates the outcomes for the group of patients without explicitly considering the outcomes of each individual patient. A cohort model may allow for some variability in patient outcome according to patient characteristics defined at the start of the model
  - Decision tree
  - Markov model, Partitioned survival model
- Patient-level simulation: a patient-level simulation as any model which estimates the mean costs and benefits for that group of patients by considering the costs and benefits of each individual within the group.

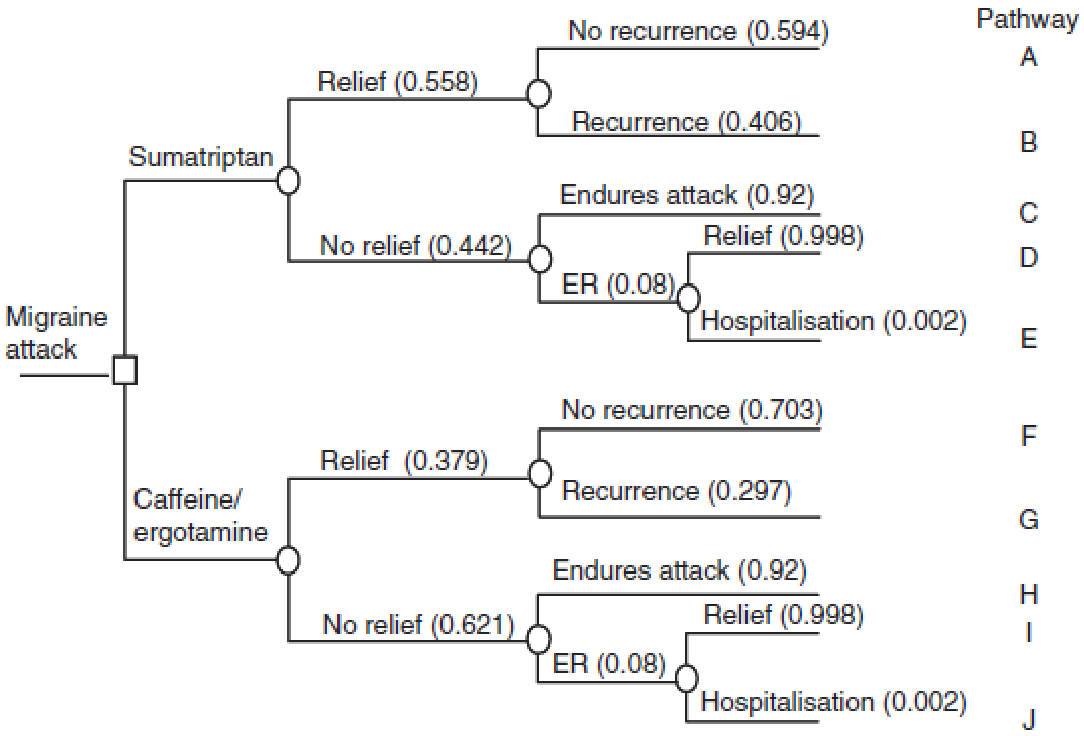
Decision Tree Model

Decision trees



Decision Tree

- Decision-analytical modeling (approaches):
  - Decision tree



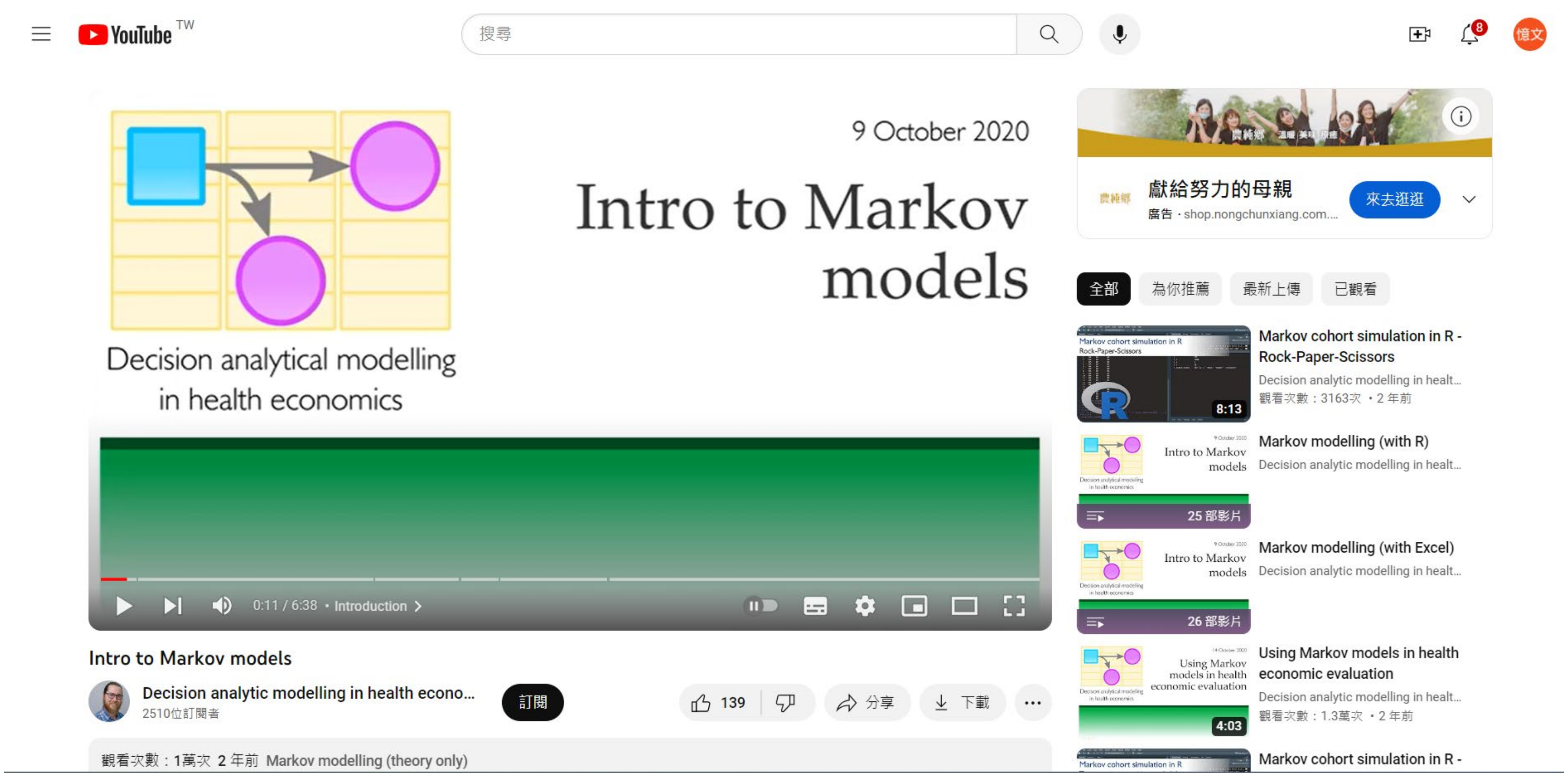
Pathway	Probability	Cost	Expected cost	Utility	Expected utility
Sumatriptan					
A	0.331	16.10	5.34	1.00	0.33
B	0.227	32.20	7.29	0.90	0.20
C	0.407	16.10	6.55	–0.30	–0.12
D	0.035	79.26	2.77	0.10	0.0035
E	0.0001	1172.00	0.11	–0.30	–0.00003
Total	**1.0000**		**22.06**		**0.41**
Caffeine/erogotamine					
F	0.266	1.32	0.35	1.00	0.27
G	0.113	2.64	0.30	0.90	0.10
H	0.571	1.32	0.75	–0.30	–0.17
I	0.050	64.45	3.22	0.10	0.0050
J	0.0001	1157.00	0.11	–0.30	–0.00003
Total	**1.0000**		**4.73**		**0.20**

Limitations of the decision tree

- Frequent need to model prognosis
- Decision trees: sequence of events over a particular time period
- Inflexible when events recur over time
- Particular difficulty in modelling chronic diseases: complications, recurrence, remission, mortality
- Decision trees may become excessively ‘bushy’

Markov Model

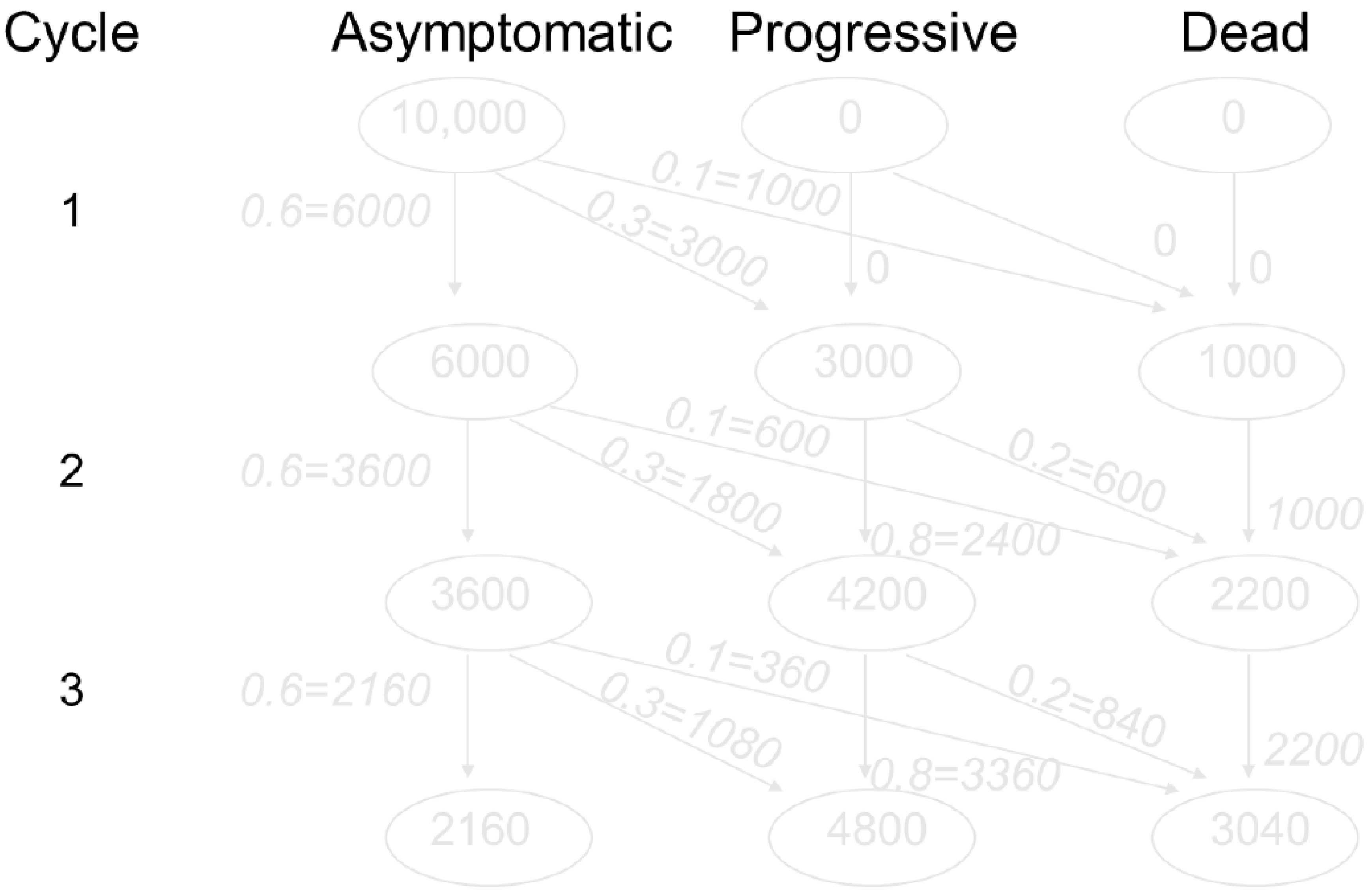
https://www.youtube.com/watch?v=d0xgyDs4EBc



The basic Markov chain

	Transition to:		
Transition from:	Asymptomatic	Progressive	Dead
Asymptomatic	0.6	0.3	0.1
Progressive	0	0.8	0.2
Dead	0	0	1

Cohort simulation
The concept



Cohort simulation

- Simulates a cohort moving through a model
- A proportion of the cohort in each state/passing down a pathway at a given point in time
- Expected values worked out by weighting these proportions by costs/outcome values
- Focus on expected values: size of cohort irrelevant

Cohort simulation
Calculating expected costs

Cycle no.	Numbers in state (total 1000)			Costs	
	Asymptomatic	Progressive	Dead	Per cycle	Cumulative
0	1000				
1	600	300	100	£30,000	£30,000
2	360	420	220	£42,000	£72,000
3	216	444	340	£44,400	£116,400
4	130	420	450	£42,000	£158,400
5	78	375	547	£37,488	£195,888
6	47	323	630	£32,323	£228,211
7	28	273	699	£27,258	£255,469
8	17	226	757	£22,646	£278,116
9	10	186	804	£18,621	£296,737
10	6	152	842	£15,199	£311,936
11	4	123	873	£12,341	£324,277
12	2	100	898	£9,981	£334,258
13	1	81	918	£8,050	£342,309
14	1	65	934	£6,480	£348,788
15	0	52	947	£5,207	£353,995
16	0	42	958	£4,180	£358,175
17	0	34	966	£3,352	£361,527
18	0	27	973	£2,687	£364,214
19	0	22	978	£2,153	£366,367
20	0	17	983	£1,724	£368,091
21	0	14	986	£1,380	£369,471
22	0	11	989	£1,105	£370,576
23	0	9	991	£884	£371,460
24	0	7	993	£708	£372,168
Expected cost/patient over 24 cycles = £372,168 /1000 = £372.17					

<u>Cost assumptions/cycle</u>

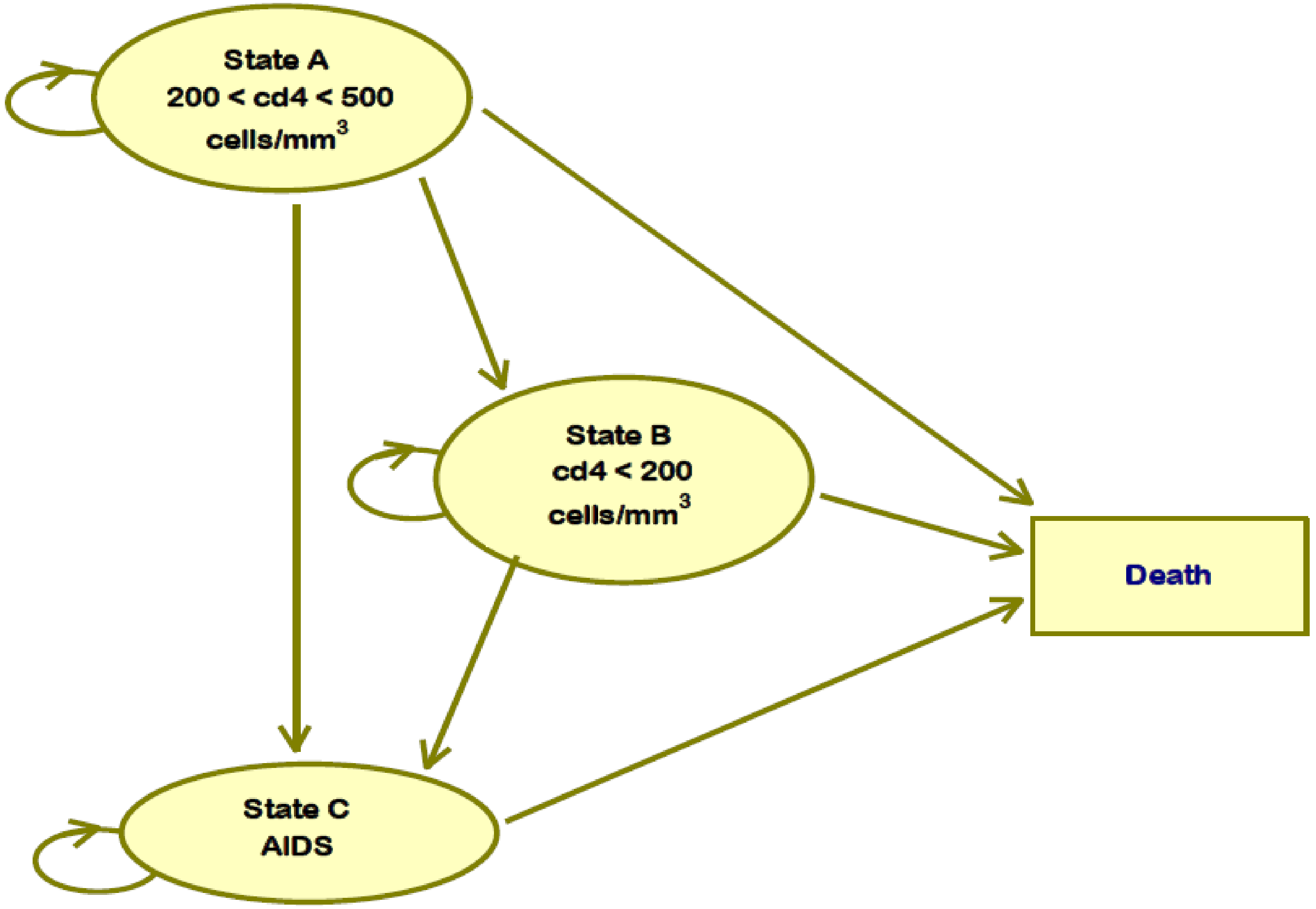
Asymptomatic: £0

Progressive: £100

Dead: £0

Example of Markov used for direct comparison

Model structure



Source: Chancellor *et al.* *PharmacoEconomics* 1997; 12: 54-66

Example of Markov used for direct comparison
Baseline transition probabilities

(a) Transition probabilities - monotherapy

	Transition to:			
Transition from:	State A	State B	State C	State D
State A	0.721	0.202	0.067	0.01
State B	0	0.581	0.407	0.012
State C	0	0	0.75	0.25
State D	0	0	0	1

Assumed a relative effect of combination therapy of 0.509. This was assumed to slow progression between all states. It was applied by reducing the yearly transitions to all worse states

Source: Chancellor *et al. PharmacoEconomics* 1997; 12: 54-66

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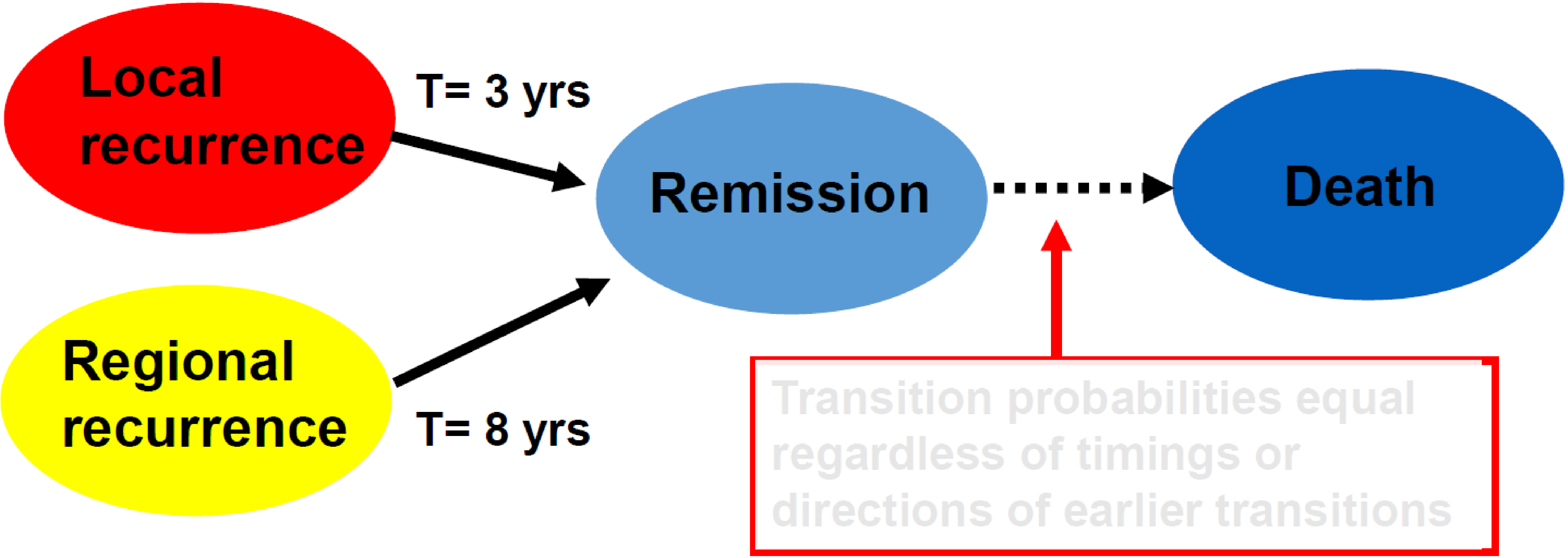
Uses of Markov models

- Estimating costs and effects for comparative interventions
  - Two sets of transition probabilities
  - Often applying a relative treatment effect to baseline transitions
- Extrapolation from trial results assuming no continued treatment effect
  - Trial estimate of treatment effect, Markov estimates the implications
  - Could be decision tree to estimate the effect (e.g. screening)

The Markov assumption



Part II: Survival Analysis

Questions

1. 甚麼是存活分析?
2. 如何分析(衡量)存活?

甚麼hazard function? 甚麼是survival function? 他們的關係是甚麼?

3. 常見的有哪些存活分析模式或函數?

- KM
- Cox Proportion Hazard models
- Exponential, Weibull and Gompertz