An integrated approach to modelling uncertainty in cost effectiveness studies: an application to the treatment of osteoporosis for secondary prevention of fractures

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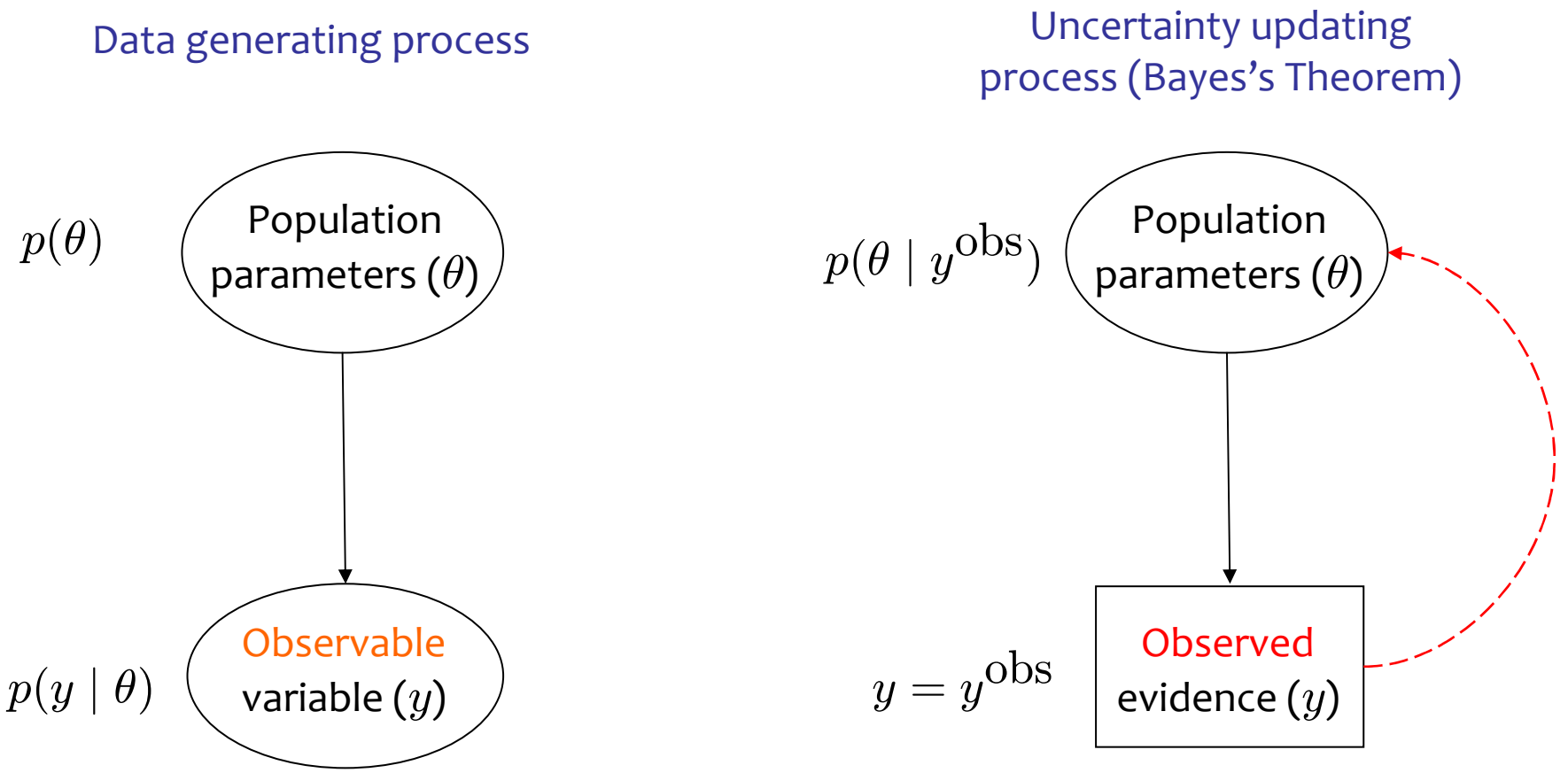
Statistical modelling

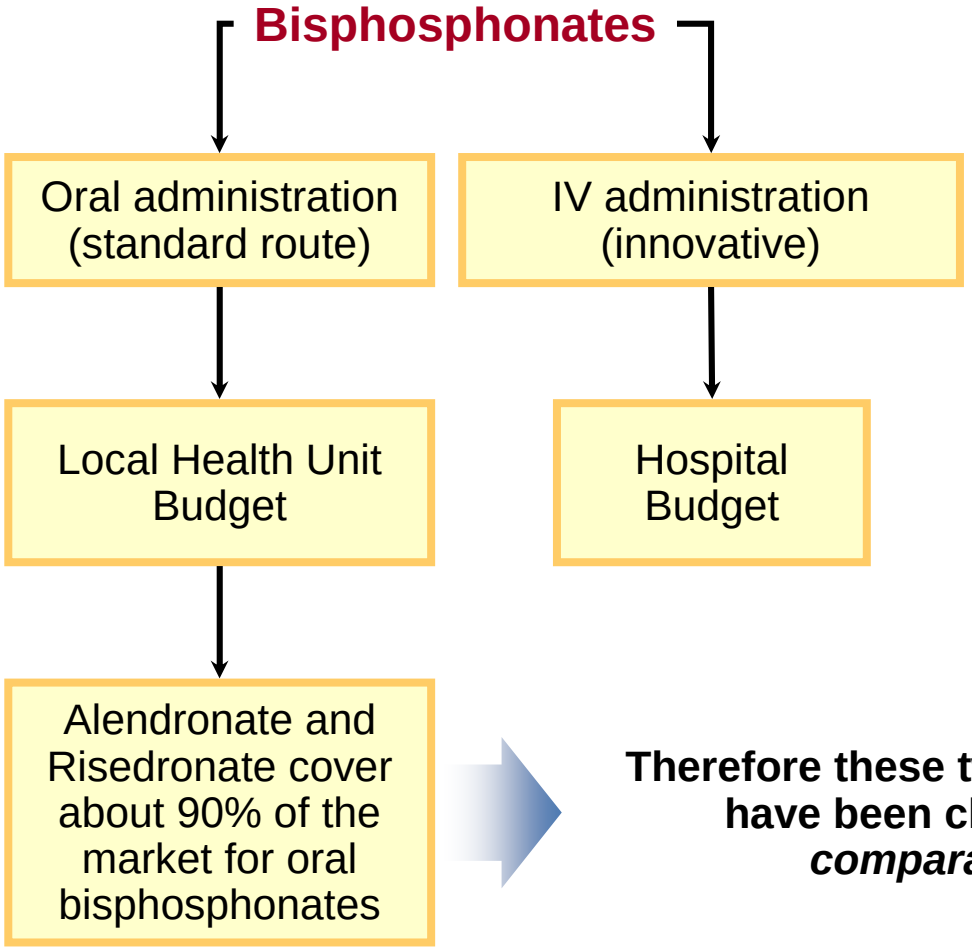
- Bayesian approach
  - (Sampling) ***variability*** vs (population) ***uncertainty***
  - All random quantities are modelled using a suitable probability distribution to describe the experimenter level of uncertainty

- Pros
  - Formal use of *all* available evidence (either hard data or expert opinion)
  - Sensitivity analysis straightforward
- Cons
  - More difficult to implement

Statistical modelling



Osteoporosis & choice of comparators



Therefore these two molecules have been chosen as *comparators*

Strontium ranelate | **Teriparatide**

- Different action mechanisms
- Direct comparability more complex

Not considered in the model

Clinical effectiveness of bisphosphonates

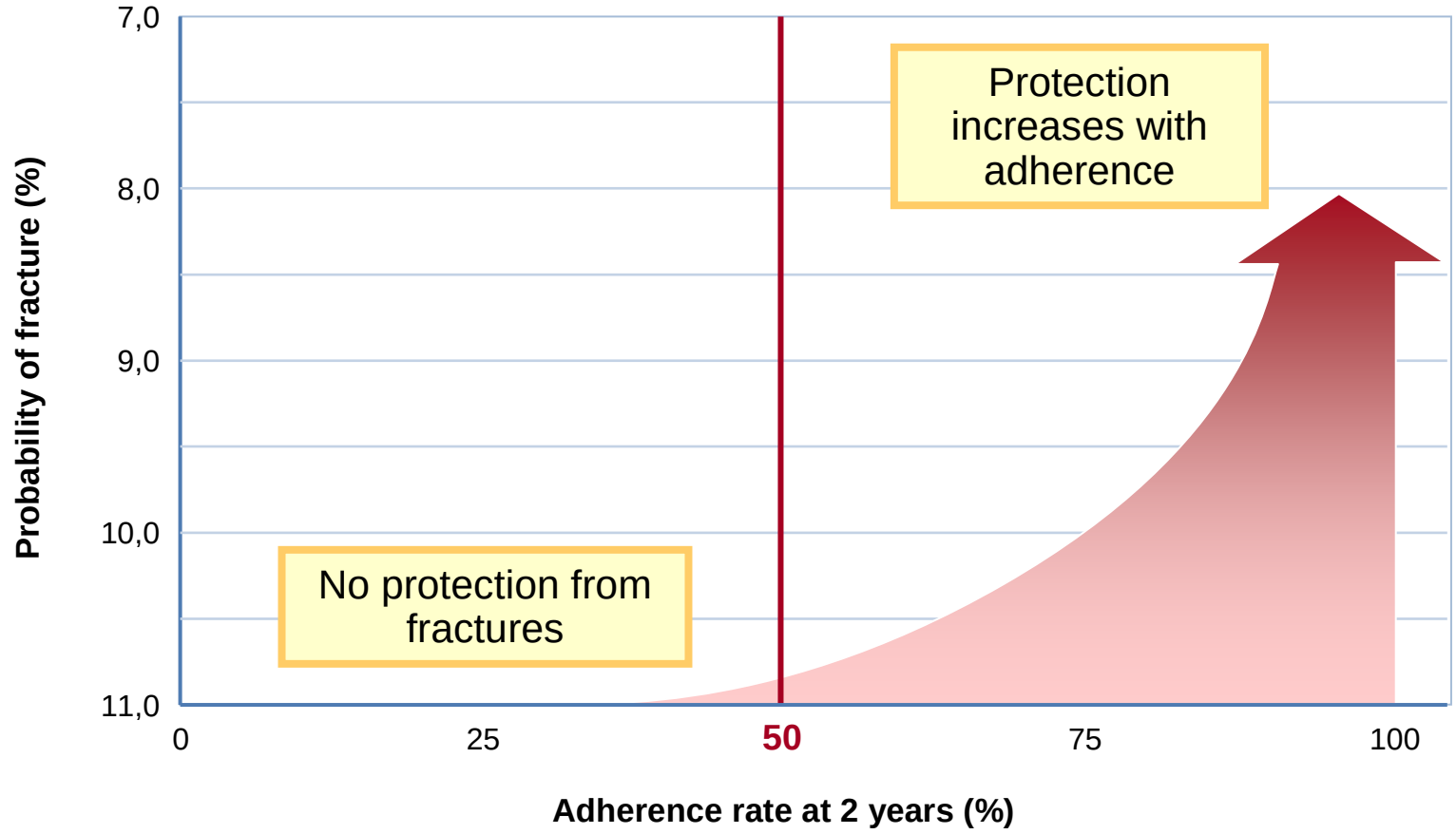
Clinical studies show effectiveness of Oral Bisphosphonates (OBs) and zoledronic acid in the reduction of fractures

	Relative risk reduction **(RRR) of fractures**		
	Wrist	***Vertebral***	***Hip***
Alendronate	19%	44%	38%
Risedronate	24%	39%	26%
Zoledronic acid	25%	70%	41%

Source: European House Ambrosetti (2007) – elab. of Stevenson et al (2005) / Black et al (2007)

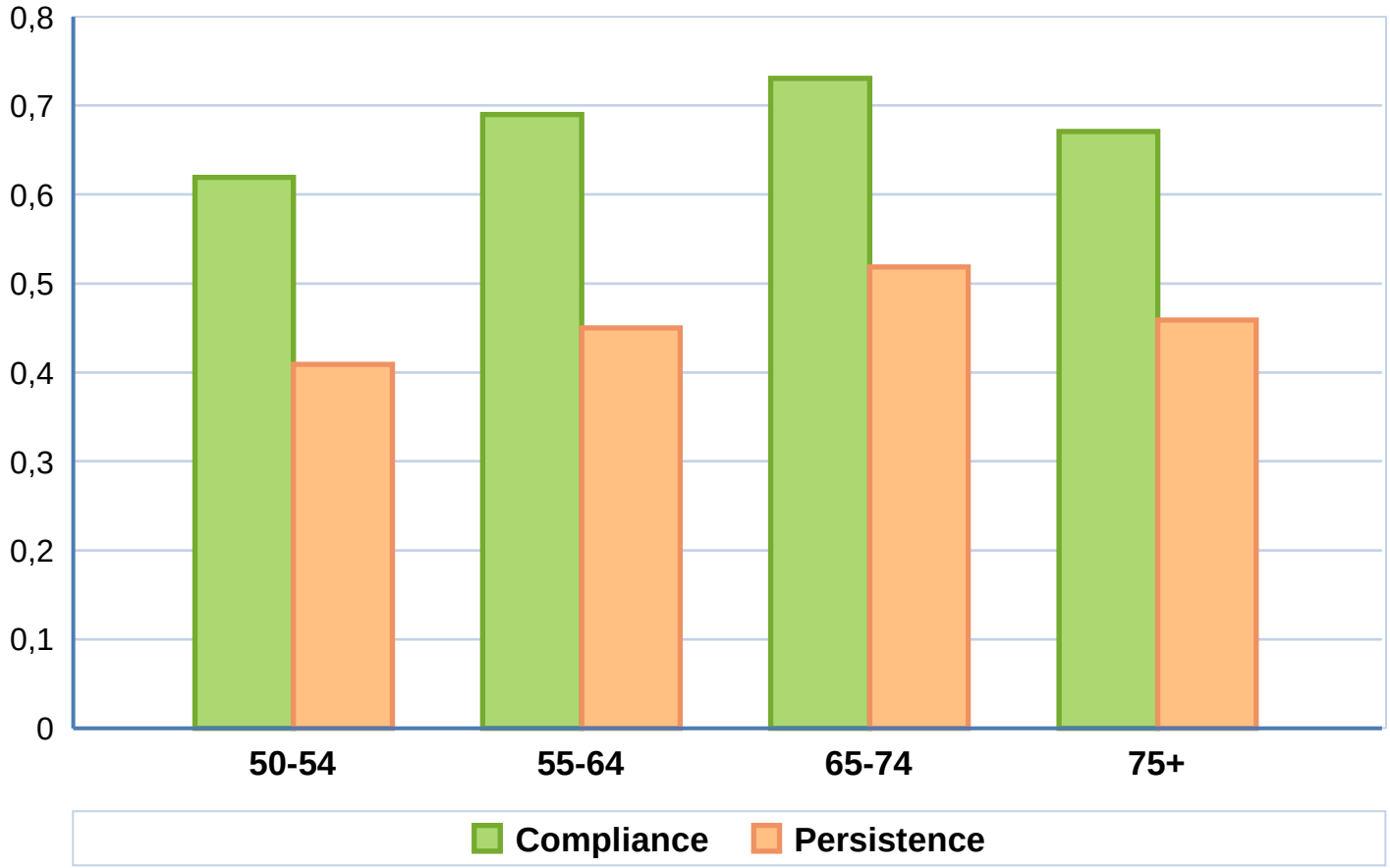
Clinical effectiveness of bisphosphonates

However, OBs are associated with low adherence with treatment, which limits their real effectiveness



Source: European House Ambrosetti (2007) – elab. of Siris et al (2006)

Compliance & Persistence with OBs (by age)



Source: our elaboration of data reported in Penning et al (2008) and Siris et al (2006)

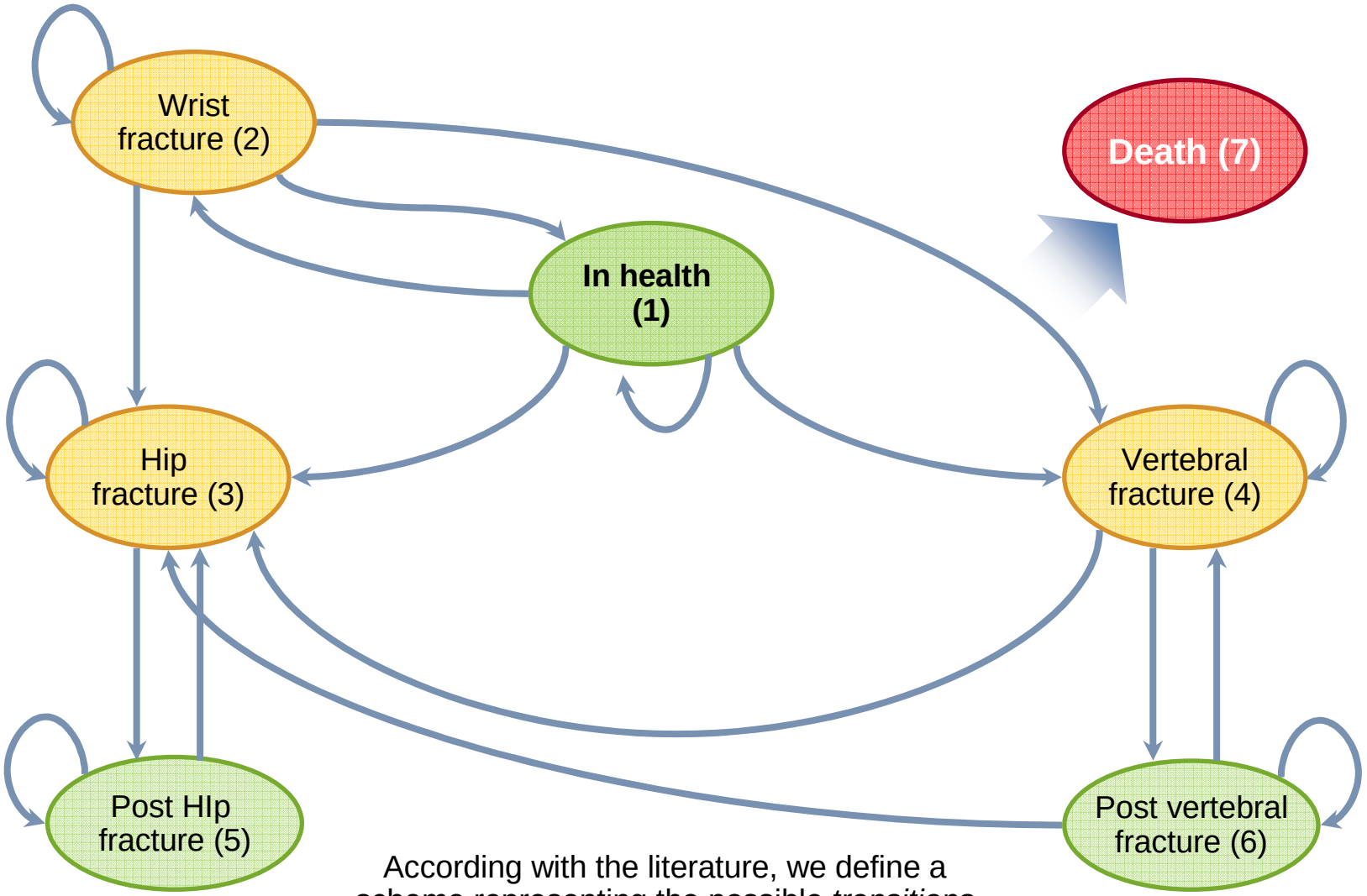
Structure of the model

- Patients can move over time between a set of ***states***
  - In health
  - Wrist fracture
  - Hip fracture
  - Vertebral fracture
  - Post Hip fracture
  - Post Vertebral fracture
  - Death

  according to pre-defined paths (eg. dead patients cannot go anywhere…), validated in the literature (Kanis et al 2004)

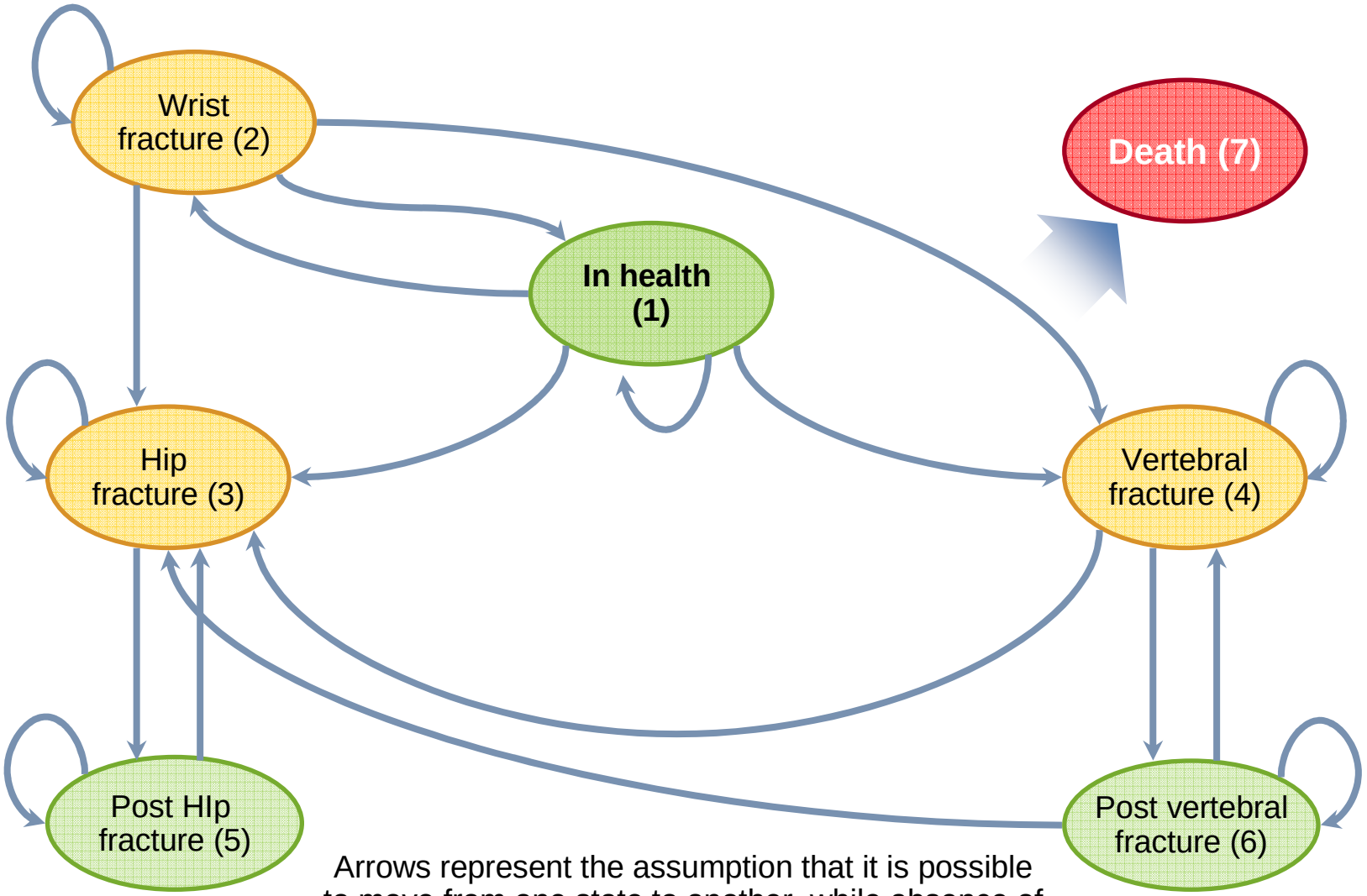
- Transition probabilities are estimated using the clinical parameters as inputs
- Age-specific values are produced (8 age categories)
- Some states are associated with a cost for the Regional Health System, RHS (ie resource utilisation, pharmacologic treatment, rehabilitation, …)

Structure of the model (2)



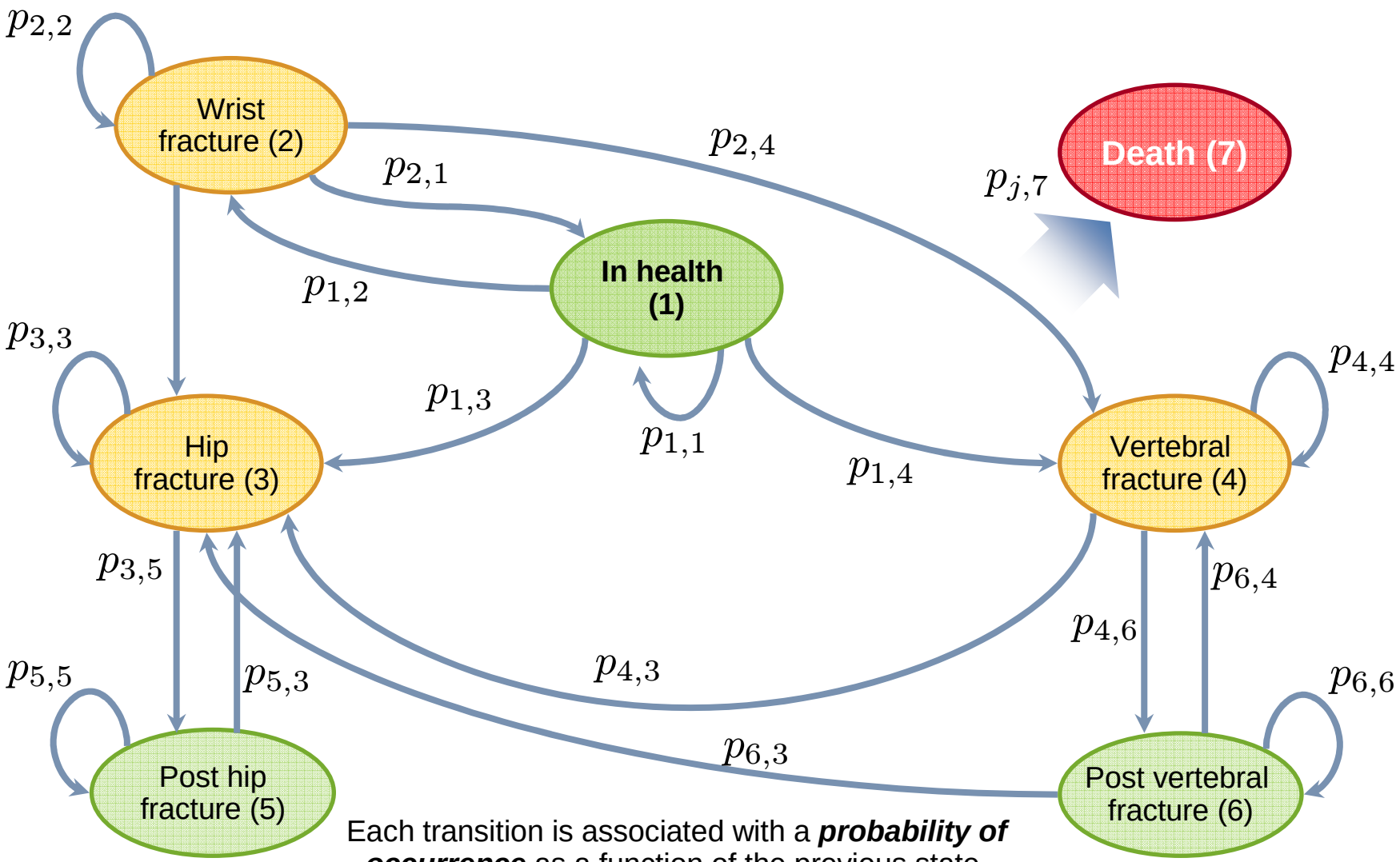
According with the literature, we define a scheme representing the possible *transitions* of the patients among the states

Structure of the model (3)



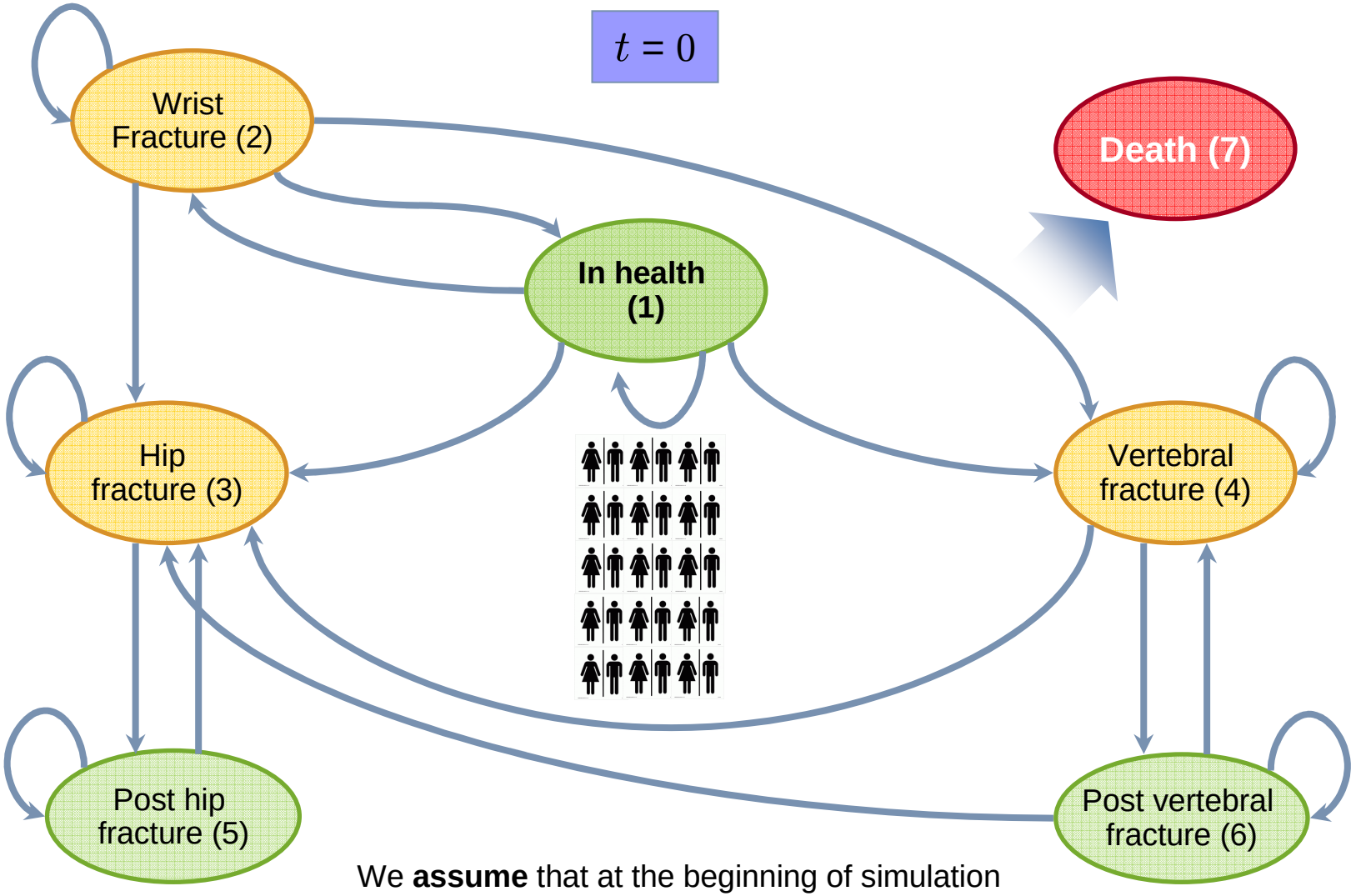
Arrows represent the assumption that it is possible to move from one state to another, while absence of arrows between two nodes encodes the assumption that the particular transition is not permitted

Structure of the model (4)



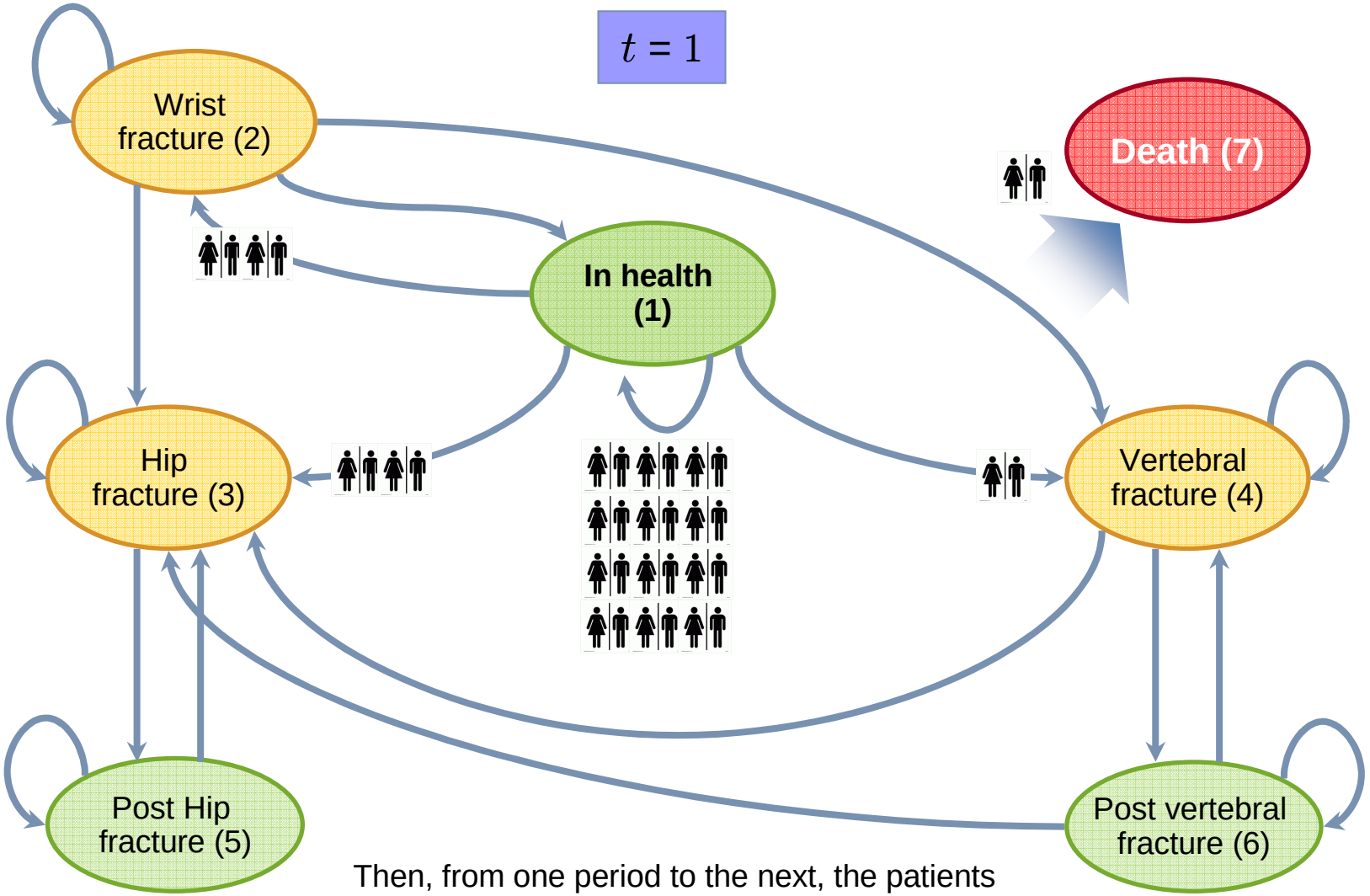
Each transition is associated with a ***probability of occurrence*** as a function of the previous state, the treatment and the age of patients

Markov model (1)



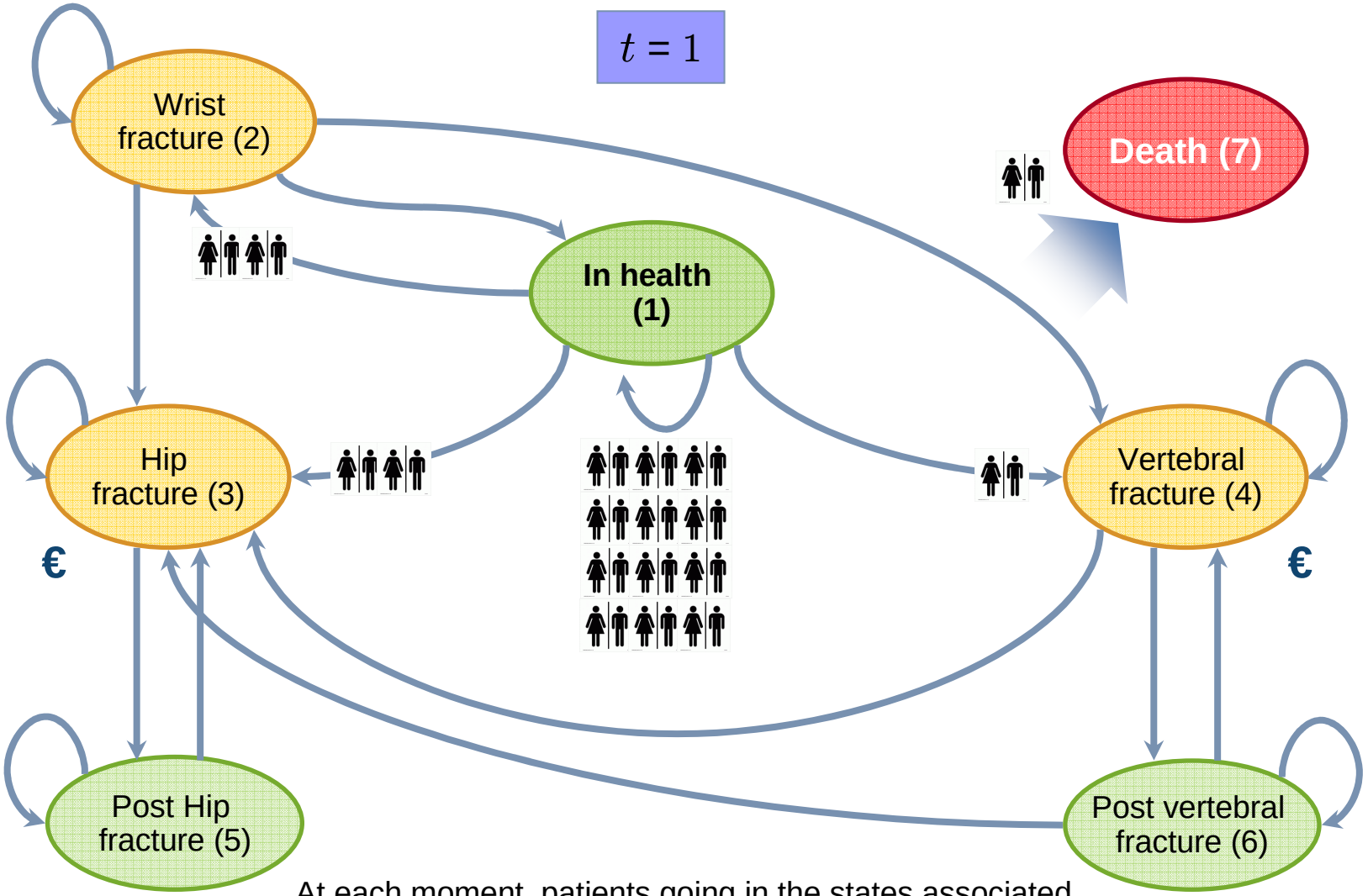
We **assume** that at the beginning of simulation ($t = 0$) all patients are in the state “In health””

Markov model (2)



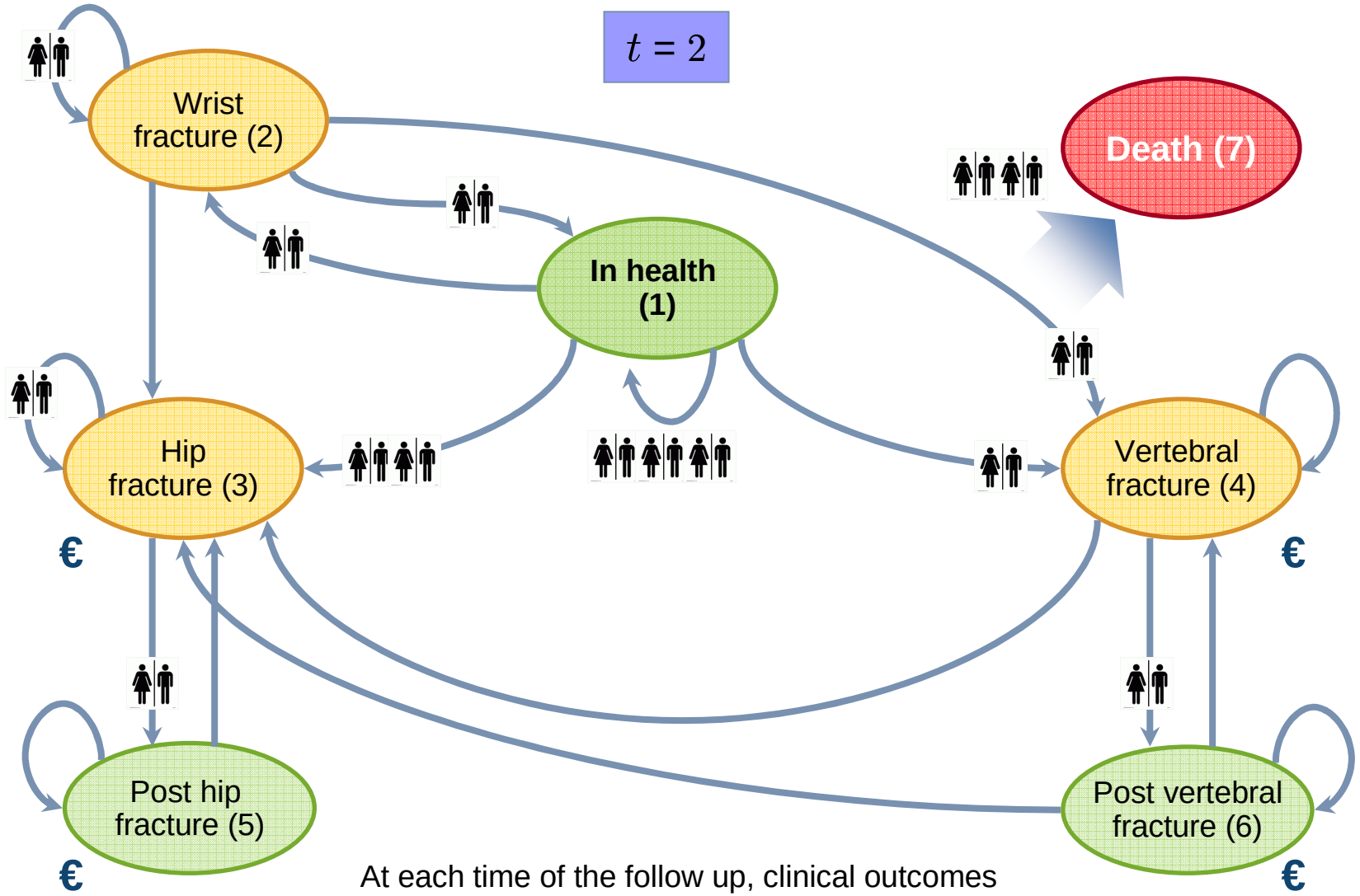
Then, from one period to the next, the patients start to move among the states, according to the transition probabilities

Markov model (3)



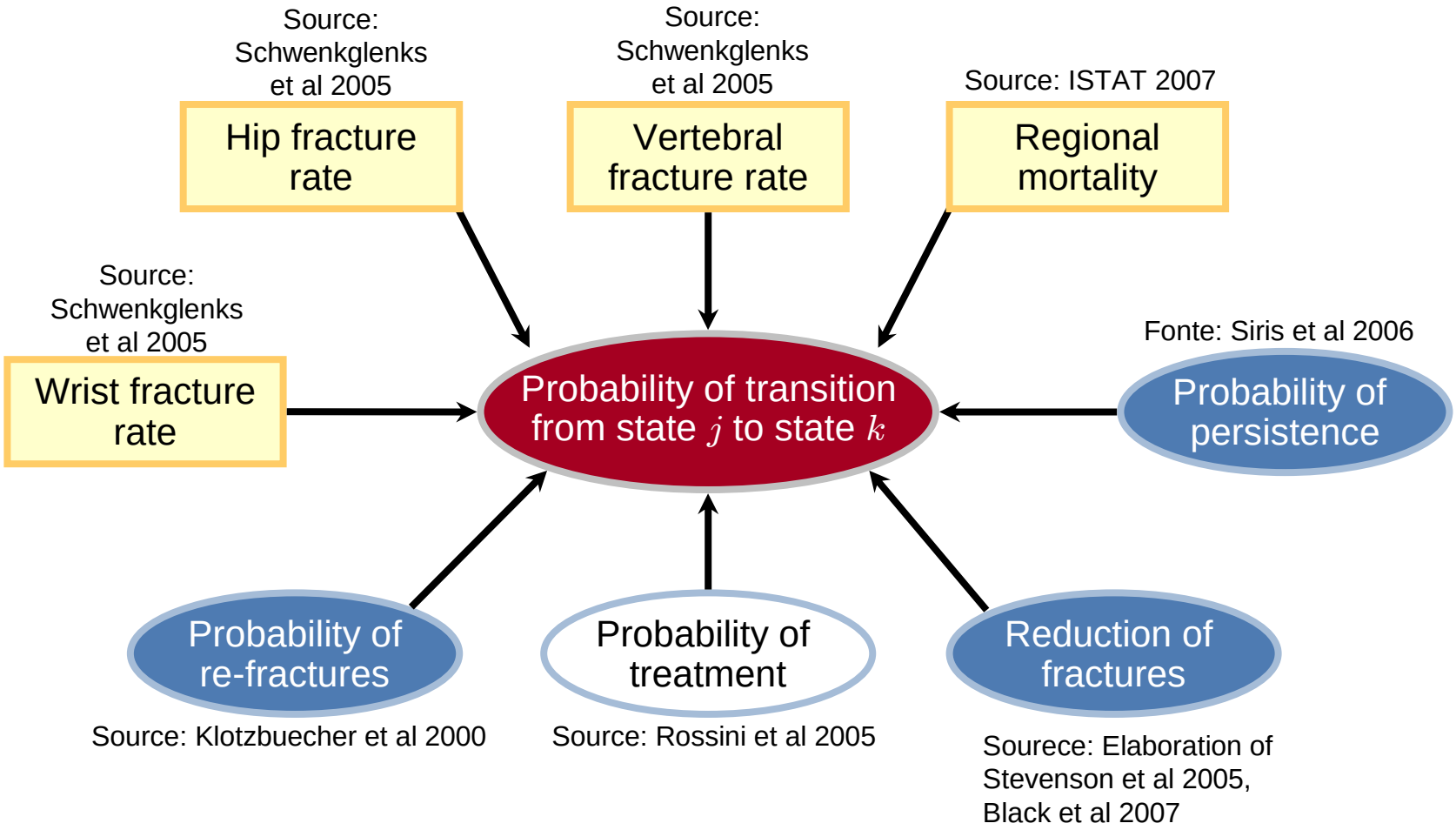
At each moment, patients going in the states associated with hip and vertebral fractures generate costs for the RHS

Markov model (4)



At each time of the follow up, clinical outcomes and costs are monitored. The simulation is run for a long “virtual” follow up

Estimation of transition probabilities p_{jk}



Observed data (literature / official sources)
Evidence integration (estimation from the model)
Expert opinion
Estimated quantities (model output)

Random quantities

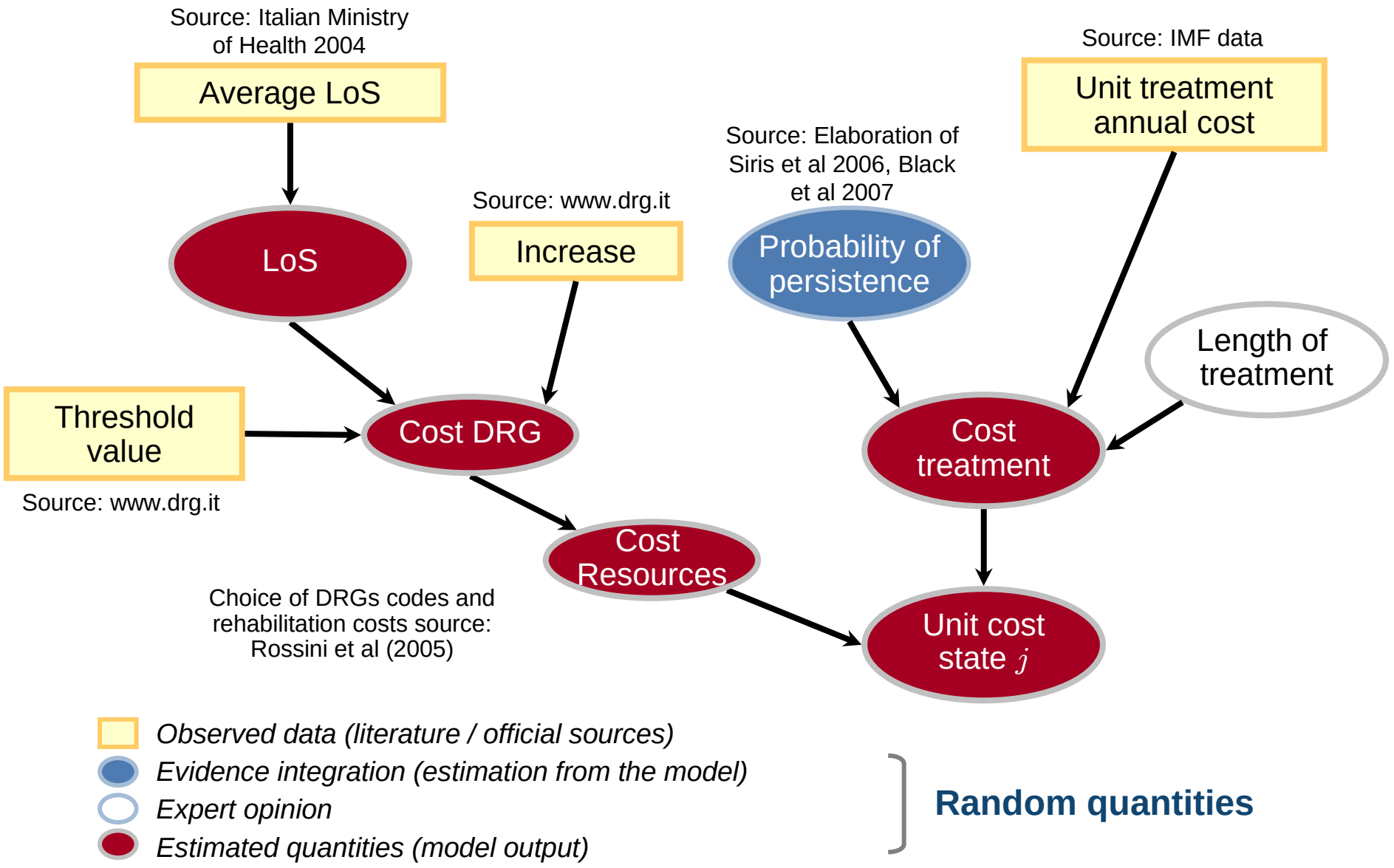
Cost of resources utilisation

- The relevant costs are
  - Hospitalisations (data at the Regions level)
  - Pharmacologic treatments (OBs vs zoledronic acid)
  - Rehab after fractures

- For OBs, persistence with treatment is reduced as suggested by the literature (Siris et al 2006)
- However, we explicitly consider the duration in treatment before the drop out (~3 months + sensitivity analysis)
- **NB Non-persistent patients do not benefit from treatment, but still incur in some (reduced) costs for the partial acquisition of the prescription**

- We consider the Regional Health System perspective (Health Technology Assessment approach), and include in the analysis the direct costs

Estimation of costs

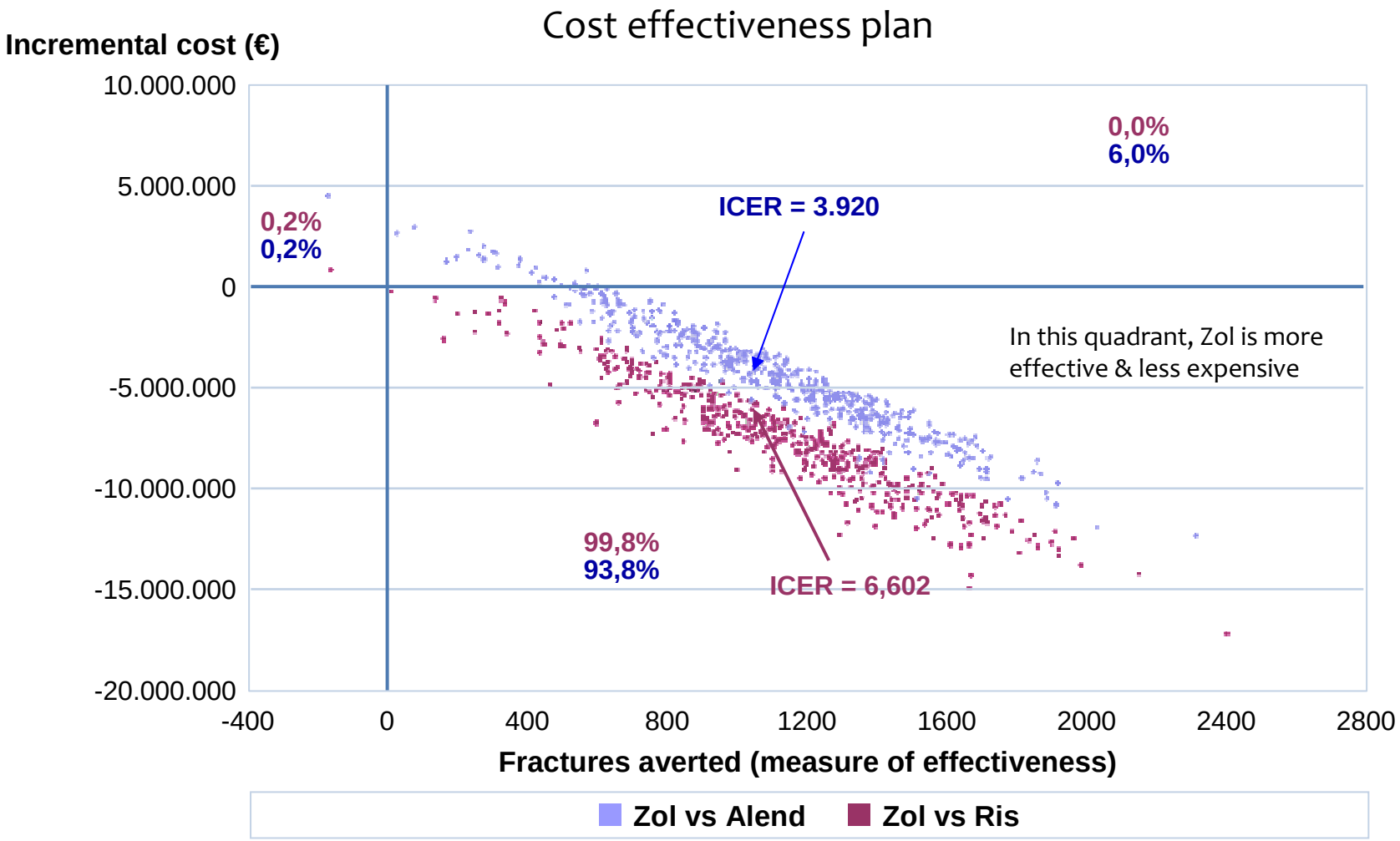


Distributional assumptions

Parameter	*Prior distribution*	*Data/expert opinion*
Population	Deterministic	Italian Statistical Office (2007)
Compliance	Flat Beta	Siris et al (2006)
Persistence	Flat Beta	Siris et al (2006)
Clinical effectiveness	Flat Beta	Stevenson et al (2006)
Mortality after hip fracture	Deterministic	Johnell et al (2005)
Mortality after surgery	Flat Beta	Franzo et al (2005)
Re-fracture	Informative lognormal	Klotzbuecher et al (2000)
Excess hip fracture after vertebral fracture	Informative lognormal	Klotzbuecher et al (2000)
Pharmacological treatment after fracture	Informative Beta	European House Ambrosetti (2008)
Mortality	Deterministic	Italian Statistical Office (2004)
Fracture rates	Flat Beta	Schwenkglenks et al (2005)
DRGs (costs)	Deterministic	Official data from RHS
Length of stay in hospital	Informative Exponential	Official data Ministry of Health

Flat (minimally informative) distributions are updated by literature data, while informative distributions are built to elicit prior knowledge (expert opinion or non-extensive literature data)

Posterior distributions analysis

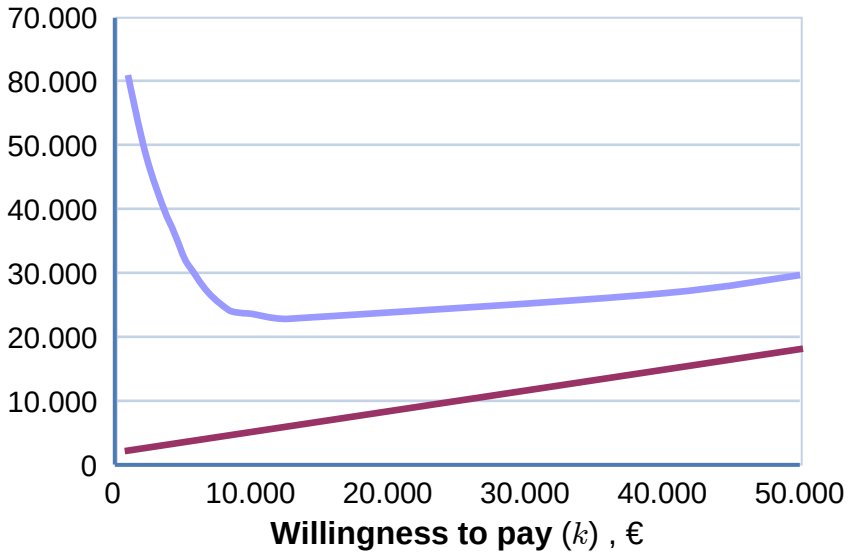


The posterior distributions can be used to produce the analysis, explicitly accounting for the uncertainty in the results

Posterior distributions analysis

Probability of cost effectiveness

Expected value of information



- For both comparisons, uncertainty about cost effectiveness of Zoledronic Acid seems to be limited

Advantages of Bayesian analysis

- Allows the formal integration of different sources of information
  - Prior literature on similar studies/drugs
  - Expert opinion about relevant issues

- Uncertainty about population parameters is accounted for properly, and reflects in a posterior distribution, which combines it with sampling (observed results) variability

- The use of simulation approach based on Markov Chain Monte Carlo methods allows the possibility of easily run sensitivity analysis to parameter uncertainty

- Posterior results of the current studies can be integrated with further data, if they become available in the form of a new informed prior distribution
  - "Today's posterior is tomorrow's prior"

Thank you!