

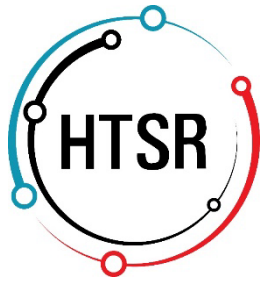


R-HTA LMIC Workshop

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PhD Candidate Health Economics

21 June 2022



Learning goals

Learning goals:

1. Understand the theory behind Markov cohort models
2. Have an overview of the setup of the DARTH cohort model in R
3. Be able to adapt the DARTH cohort model to a new model

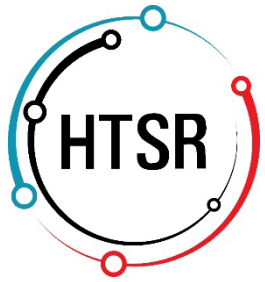
Assumed preknowledge:

1. Rationale behind health economic evaluations
2. Concept of utilities and QALYs
3. Estimation of ICER
4. Simple decision tree approaches to modelling



PART 1

Markov cohort Models

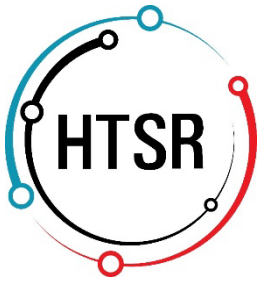


Cohort state-transition model

- Hypothetical cohort transitioning through health states
- Group result is represented by a single number
- Memoryless (Markovian assumption)
- Health states are mutually exclusive and collectively exhaustive
- Cohort is homogenous within each health state

An Introductory Tutorial on Cohort State-Transition Models in R Using a Cost-Effectiveness Analysis Example

[Fernando Alarid-Escudero](#), [Eline M. Krijkamp](#), [Eva A. Enns](#), [Alan Yang](#), [M.G. Myriam Hunink](#), [Petros Pechlivanoglou](#), [Hawre Jalal](#)



Case study: Sick sicker

Cohort 25-year-old
Time horizon; Max age = 100
Cycle length = 1 year

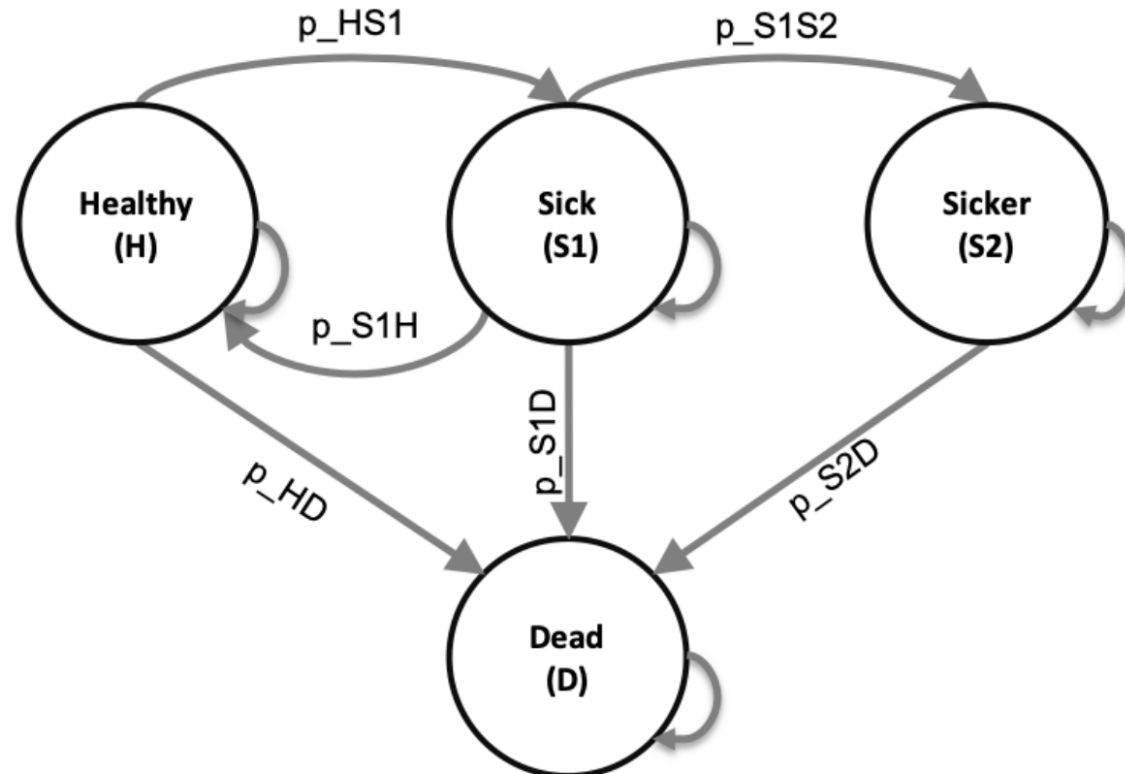
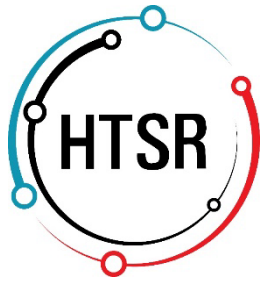


Figure 1: State-transition diagram of the time-independent Sick-Sicker cohort state transition model with the name of the health states and possible transitions with their corresponding transition probability names



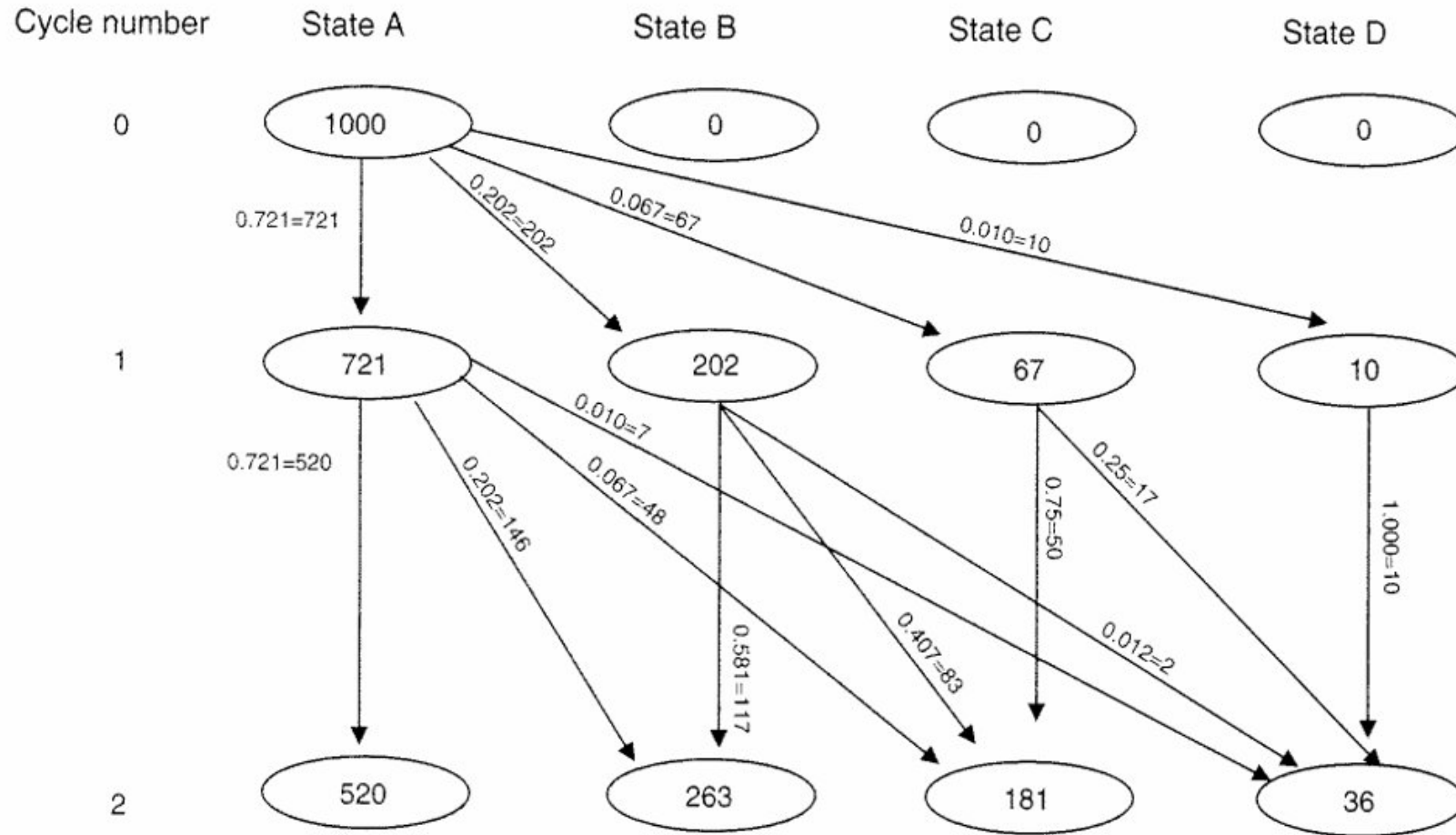
Transition probability matrix

	Healthy	Sick	Sicker	Death
Healthy	0,722	0,207	0,061	0,01
Sick	0	0,582	0,401	0,017
Sicker	0	0	0,74	0,26
Death	0	0	0	1

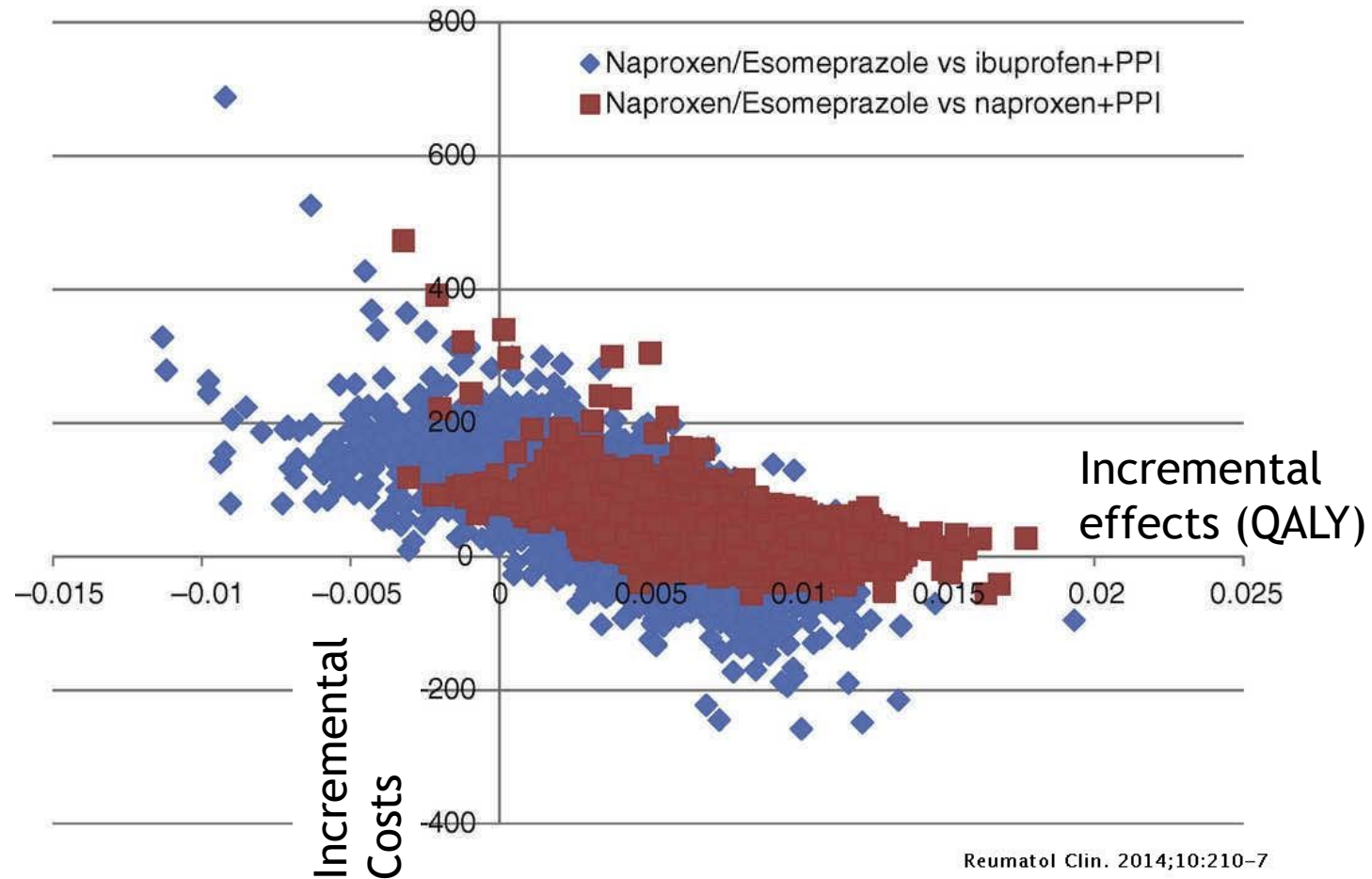
→ = 1

Different transition probability matrices for strategies

Illustrative example



ICER Plane

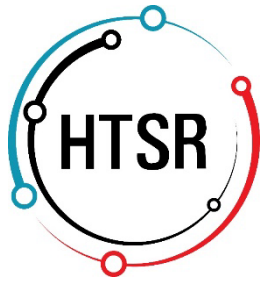




PART 2

DARTH cohort

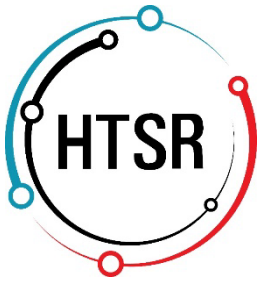
Model



DARTH discrete-time cohort state-transition model (cSTM)



- Referred to as Markov model
- We will look at time-independent model
- Repositories from DARTH workgroup:
 - Microsimulation-tutorial
 - Dampack : Decision Analytic Modeling package
 - Cohort-modeling-tutorial
 - Darthpack: Decision Analytic Modeling Coding Framework
- Alarid-Escudero, Fernando, et al. "An Introductory Tutorial on Cohort State-Transition Models in R Using a Cost-Effectiveness Analysis Example." *arXiv preprint arXiv:2001.07824* (2020).



Variables

`<x>_<y>_<var_name>`



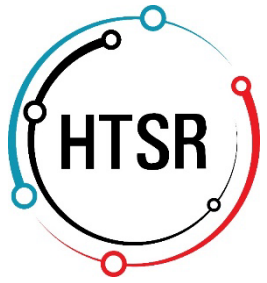
Data type:

- : Scalar
- v: Vector
- m: Matrix
- a: Array
- df: Dataframe

Variable type:

- p: probability
- r: rate
- hr: hazard ratio
- Lor: log-odds ratio
- c: cost
- u: utility

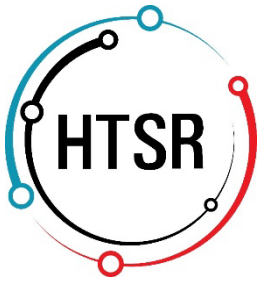
Description



Variables: Examples

`<x>_<y>_<var_name>`

c_H
r_HD
u_S2
p_HS1
v_s_init



Variables: Examples

`<x>_<y>_<var_name>`

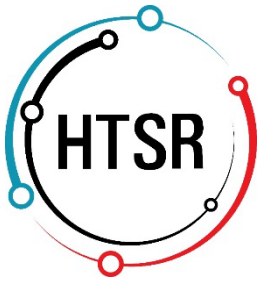
c_H -> Cost of being in the healthy state

r_HD -> rate of moving from healthy to death = baseline mortality rate

u_S2 -> Utility of being sicker

p_HS1 -> probability of moving from healthy to sick

v_s_init -> vector containing the initial proportion of individuals in each state

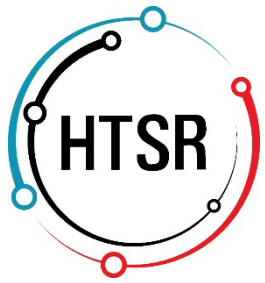


R code- Introduction of parameters

```
## General setup
cycle_length <- 1 # cycle length equal one year
n_age_init <- 25 # age at baseline
n_age_max <- 100 # maximum age of follow up
n_cycles <- n_age_max - n_age_init # number of cycles
v_names_states <- c("H", "S1", "S2", "D") # the 4 health states of the model:
                                         # Healthy (H), Sick (S1), Sicker (S2), Dead (D)

n_states <- length(v_names_states) # number of health states
d_e <- 0.03 # discount rate for QALYs of 3% per cycle
d_c <- 0.03 # discount rate for costs of 3% per cycle
v_names_str <- c("Standard of care", # store the strategy names
                "Strategy A",
                "Strategy B",
                "Strategy AB")

## Transition probabilities (per cycle), hazard ratios and odds ratio (OR)
r_HD <- 0.002 # constant rate of dying when Healthy (all-cause mortality rate)
p_HS1 <- 0.15 # probability of becoming Sick when Healthy
p_S1H <- 0.5 # probability of becoming Healthy when Sick
p_S1S2 <- 0.105 # probability of becoming Sicker when Sick
hr_S1 <- 3 # hazard ratio of death in Sick vs Healthy
hr_S2 <- 10 # hazard ratio of death in Sicker vs Healthy
```



R code - Transform rates to probabilities (using function)

```
## Probabilities of dying
```

```
cycle_length <- 1
```

```
p_HD <- 1 - exp(-r_HD*cycle_length)
```

```
p_S1D <- 1 - exp(-r_S1D*cycle_length)
```

```
p_S2D <- 1 - exp(-r_S2D*cycle_length)
```

```
## transform rates to probabilities
```

```
## Function included in "R/Functions.R". The latest
```

```
p_HS1 <- rate_to_prob(r = r_HS1, t = cycle_length)
```

```
p_S1H <- rate_to_prob(r = r_S1H, t = cycle_length)
```

```
p_S1S2 <- rate_to_prob(r = r_S1S2, t = cycle_length)
```

```
p_HD <- rate_to_prob(r = r_HD, t = cycle_length)
```

```
p_S1D <- rate_to_prob(r = r_S1D, t = cycle_length)
```

```
p_S2D <- rate_to_prob(r = r_S2D, t = cycle_length)
```

```
## Convert a rate to a probability
```

```
##
```

```
## \code{rate_to_prob} convert a rate to a probability.
```

```
##
```

```
## @param r rate
```

```
## @param t time/ frequency
```

```
## @return a scalar or vector with probabilities
```

```
## @examples
```

```
## # Annual rate to monthly probability
```

```
## r_year <- 0.3
```

```
## r_month <- rate_to_prob(r = r_year, t = 1/12)
```

```
## r_month
```

```
## @export
```

```
rate_to_prob <- function(r, t = 1){
```

```
  if ((sum(r < 0) > 0)){
```

```
    stop("rate not greater than or equal to 0")
```

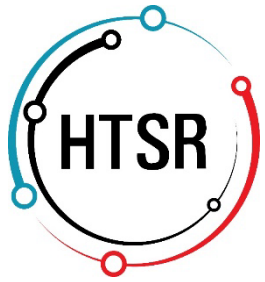
```
  }
```

```
  p <- 1 - exp(- r * t)
```

```
  return(p)
```

```
}
```

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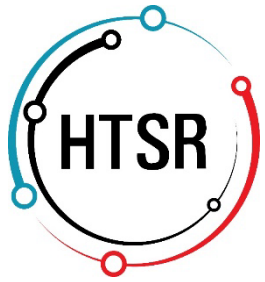
R code- Variables (1)

$$M = \begin{bmatrix} -\mathbf{m}_0- \\ -\mathbf{m}_1- \\ \vdots \\ -\mathbf{m}_{n_T}- \end{bmatrix}.$$

$$\mathbf{m}_t = \begin{bmatrix} m_{[t,1]} & m_{[t,2]} & \cdots & m_{[t,n_S]} \end{bmatrix}$$

State vector: Stores the distribution of the cohort across all states
Cohort trace matrix M

		States			
Cycles		H	S1	S2	D
	0	1.0000000	0.00000000	0.00000000	0.000000000
	1	0.8589883	0.13901372	0.00000000	0.001998001
	2	0.7922313	0.18944948	0.01377337	0.004545846
	3	0.7546140	0.20558006	0.03227115	0.007534750



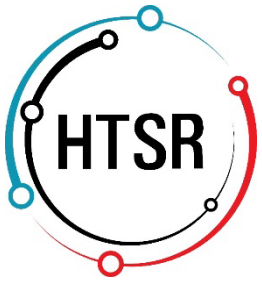
R code- Variables (2)

$$P = \begin{bmatrix} p_{[1,1]} & p_{[1,2]} & \cdots & p_{[1,n_S]} \\ p_{[2,1]} & p_{[2,2]} & \cdots & p_{[2,n_S]} \\ \vdots & \vdots & \ddots & \vdots \\ p_{[n_S,1]} & p_{[n_S,2]} & \cdots & p_{[n_S,n_S]} \end{bmatrix}$$

Transition probability matrix

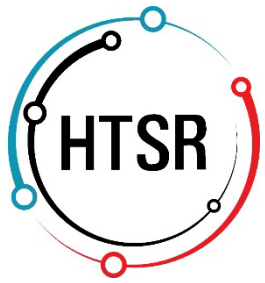
Elements of transition probabilities: Moving from state i to j

	H	S1	S2	D
H	0.8589883	0.1390137	0.00000000	0.001998001
S1	0.3911156	0.5038232	0.09907922	0.005982036
S2	0.0000000	0.0000000	0.98019867	0.019801327
D	0.0000000	0.0000000	0.00000000	1.000000000

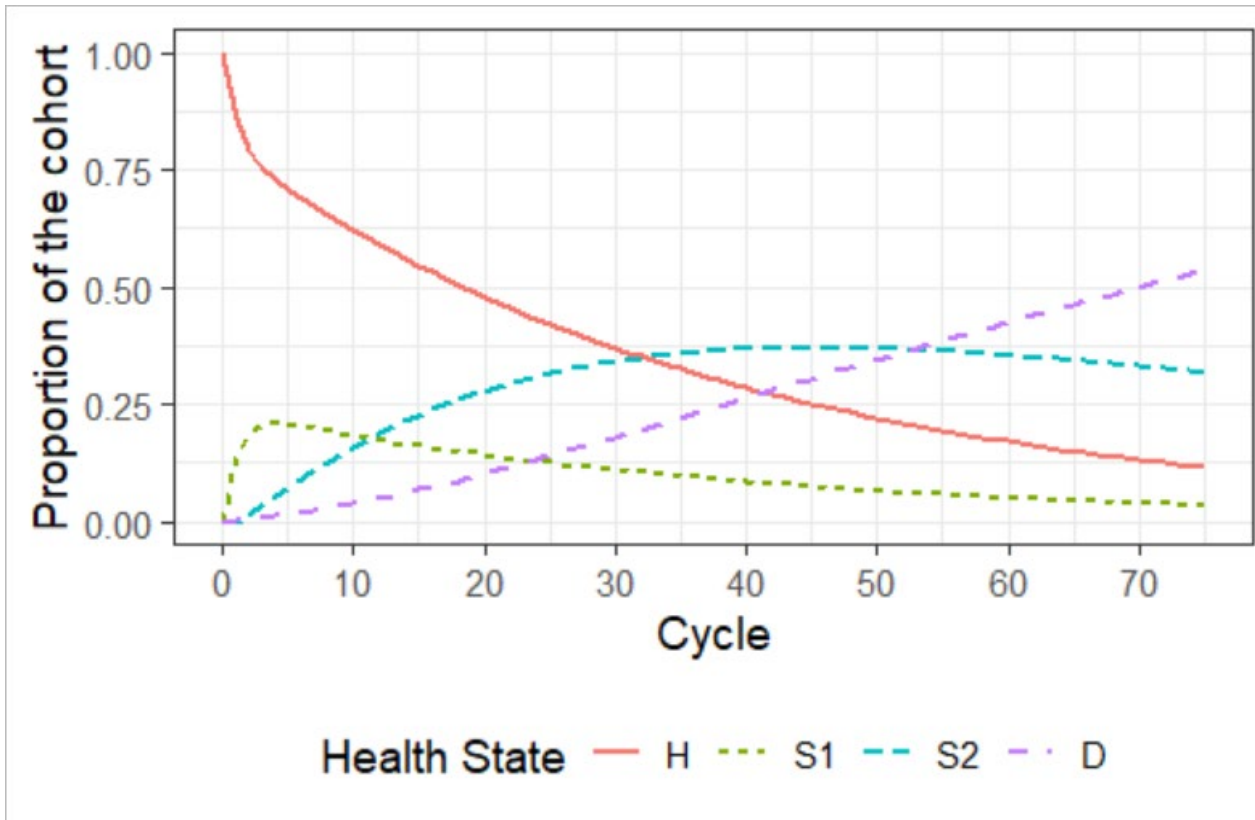


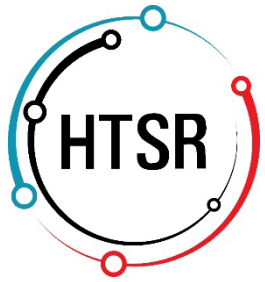
Run the model

```
# Run Markov model ----  
#* Iterative solution of time-independent cSTM  
for(t in 1:n_cycles){  
  # For SoC  
  m_M[t + 1, ] <- m_M[t, ] %*% m_P  
  # For strategy A  
  m_M_strA[t + 1, ] <- m_M_strA[t, ] %*% m_P_strA  
  # For strategy B  
  m_M_strB[t + 1, ] <- m_M_strB[t, ] %*% m_P_strB  
  # For strategy AB  
  m_M_strAB[t + 1, ] <- m_M_strAB[t, ] %*% m_P_strAB  
}
```



Plots





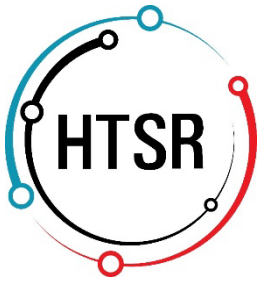
Within Cycle Correction and discounting

WCC

Simpson's 1/3rd rule

Discounting

Cycle-length rate can be set for costs and effects separately

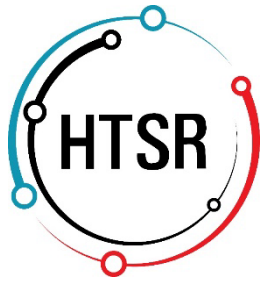


Calculate outcomes

```
## Loop through each strategy and calculate total utilities and costs ----
for (i in 1:n_str) {
  v_u_str <- l_u[[i]] # select the vector of state utilities for the i-th strategy
  v_c_str <- l_c[[i]] # select the vector of state costs for the i-th strategy

  ####* Expected QALYs and costs per cycle
  ##* Vector of QALYs and Costs
  ##* Apply state rewards
  v_qaly_str <- l_m_M[[i]] %*% v_u_str # sum the utilities of all states for each strategy
  v_cost_str <- l_m_M[[i]] %*% v_c_str # sum the costs of all states for each strategy

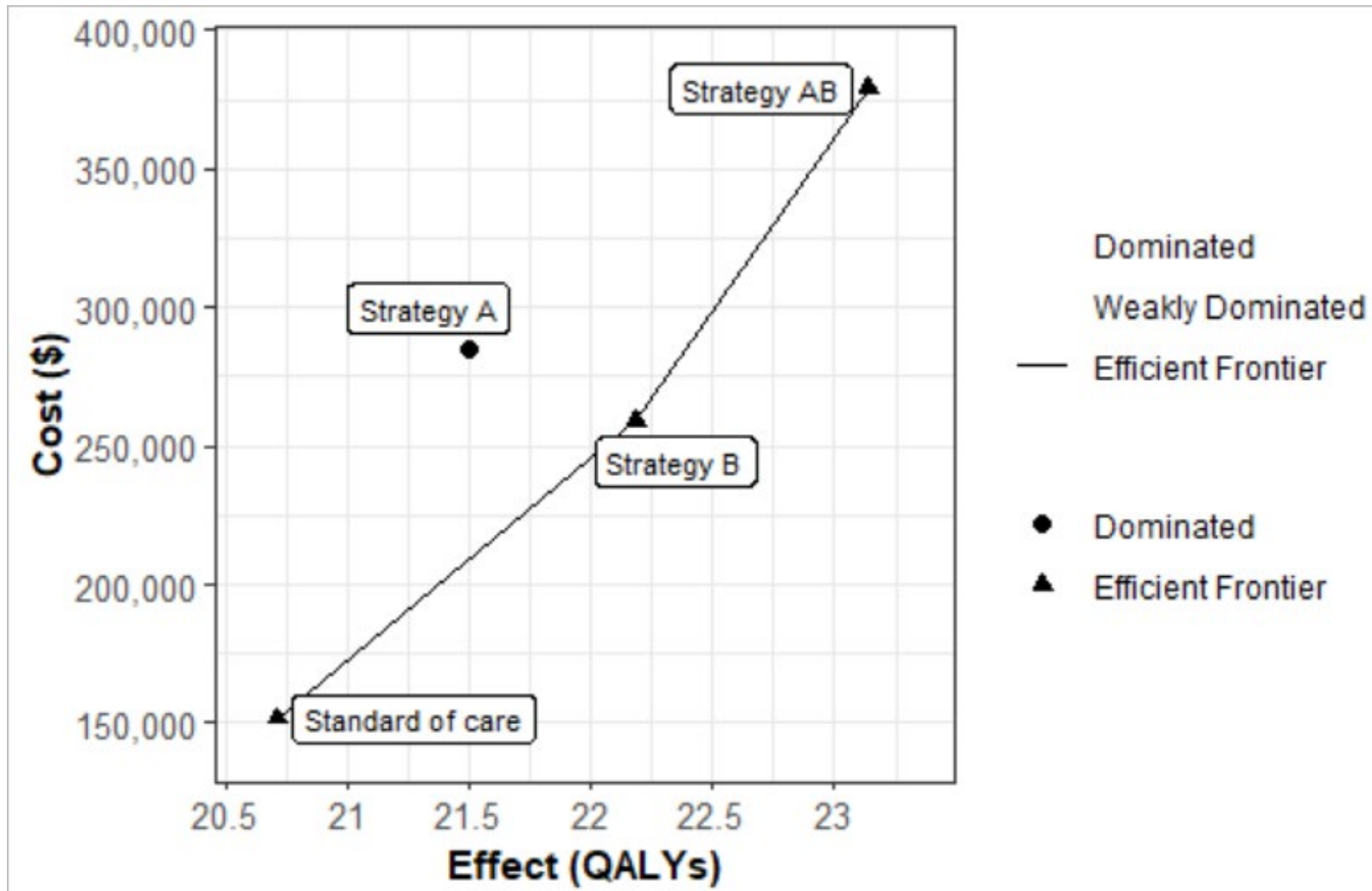
  #####* Discounted total expected QALYs and Costs per strategy and apply half-cycle correction
  ##* QALYs
  v_tot_qaly[i] <- t(v_qaly_str) %*% (v_dwe * v_wcc)
  ##* Costs
  v_tot_cost[i] <- t(v_cost_str) %*% (v_dwc * v_wcc)
}
```

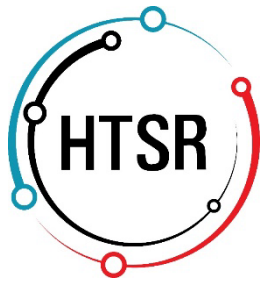


Calculate outcomes

```
# Cost-effectiveness analysis (CEA) ----  
## Incremental cost-effectiveness ratios (ICERs) ----  
#* Function included in "R/Functions.R"; depends on the `dplyr` package  
#* The latest version can be found in dampack package  
df_cea <- calculate_icers(cost      = v_tot_cost,  
                          effect    = v_tot_qaly,  
                          strategies = v_names_str)  
  
df_cea
```

ICER plane

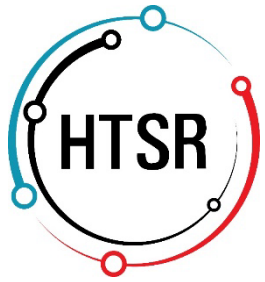




Questions to answer

1. What is the annual probability of becoming "Sick" (S1) while in the "Healthy" (H) stage?
2. And the probability of entering "Sicker" (S2) while in the "Sick" stage (S1), under Therapy B?
3. How many matrices did you create to obtain the entire cohort distribution between the different states through the whole analysis time horizon for "Strategy A"? And for all strategies?
4. For "Strategy AB": how many patients (out of 100) were at the "Health (H)" state during the last cycle (year 75 of follow-up)? And For "Strategy A"?
5. What were the total discounted costs and QALYs for "Strategy B" for the entire time horizon of analysis?

1. ¿Cuál es el valor calculado de la probabilidad anual de volverse "Enfermo (S1)" estando en estadio "Sano (H)"?
2. ¿Y la probabilidad anual de pasar al estadio "Enfermo Severo (S2)" estando en estadio Enfermo (S1), bajo la Terapia B?
3. ¿Cuántas matrices ha tenido usted que crear para obtener la distribución de toda la cohorte entre los diferentes estadios a través de todo el horizonte temporal de análisis para la estrategia A? Y para todas las estrategias?
4. Para la "Estrategia AB": ¿cuántos pacientes (de un total de 100 pacientes iniciales) estuvieron en el estado "Sano (H)" durante el último ciclo (año 75 de seguimiento)? ¿Y para la "Estrategia A"?
5. ¿Cuáles fueron los costos y QALYs descontados totales para la "Estrategia B" para todo el horizonte temporal del análisis?



Questions to answer

1. p_HS1: 0.139292.
2. p_S1S2_trtB: 0.06105653.
3. For “Strategy A”: two (2) matrices. For all the strategies: eight (8) matrices.
4. For Strategy AB = approx. 21 patients out of 100 (exactly: 20.7)
For Strategy A = approx. 12 out of 100 (exactly: 11.5)
5. Strategy B: Costs = 259100; QALYs = 22.18447