

3-state Markov model in R

With simulation-time dependency and sensitivity analysis

The DARTH workgroup

Developed by the Decision Analysis in R for Technologies in Health (DARTH) workgroup:

Fernando Alarid-Escudero, PhD (1)

Eva A. Enns, MS, PhD (2)

M.G. Myriam Hunink, MD, PhD (3,4)

Hawre J. Jalal, MD, PhD (5)

Eline M. Krijkamp, MSc (3)

Petros Pechlivanoglou, PhD (6,7)

Alan Yang, MSc (7)

In collaboration of:

1. Division of Public Administration, Center for Research and Teaching in Economics (CIDE), Aguascalientes, Mexico
2. University of Minnesota School of Public Health, Minneapolis, MN, USA
3. Erasmus MC, Rotterdam, The Netherlands
4. Harvard T.H. Chan School of Public Health, Boston, USA
5. University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA
6. University of Toronto, Toronto ON, Canada
7. The Hospital for Sick Children, Toronto ON, Canada

Please cite our publications when using this code:

- Alarid-Escudero F, Krijkamp EM, Enns EA, Yang A, Hunink MGM Pechlivanoglou P, Jalal H. A Tutorial on Time-Dependent Cohort State-Transition Models in R using a Cost-Effectiveness Analysis Example. *Medical Decision Making*, 2022 (In press): 1-21. <https://doi.org/10.1177/0272989X221121747>
- Alarid-Escudero F, Krijkamp EM, Enns EA, Yang A, Hunink MGM Pechlivanoglou P, Jalal H. An Introductory Tutorial on Cohort State-Transition Models in R Using a Cost-Effectiveness Analysis Example. *Medical Decision Making*, 2022 (Online First):1-18. <https://doi.org/10.1177/0272989X221103163>
- Alarid-Escudero F, Krijkamp EM, Enns EA, Yang A, Hunink MGM Pechlivanoglou P, Jalal H. An Introductory Tutorial on Cohort State-Transition Models in R Using a Cost-Effectiveness Analysis Example. *Medical Decision Making*, 2022 (Online First):1-18. <https://doi.org/10.1177/0272989X221103163>
- Jalal H, Pechlivanoglou P, Krijkamp E, Alarid-Escudero F, Enns E, Hunink MG. An Overview of R in Health Decision Sciences. *Med Decis Making*. 2017; 37(3): 735-746. <https://journals.sagepub.com/doi/abs/10.1177/0272989X16686559>
- Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. *Med Decis Making*. 2018;38(3):400-22. <https://journals.sagepub.com/doi/abs/10.1177/0272989X18754513>

- Krijkamp EM, Alarid-Escudero F, Enns E, Pechlivanoglou P, Hunink MM, Jalal H. A Multidimensional Array Representation of State-Transition Model Dynamics. *Med Decis Mak.* 2020;40(2):242-248. <https://doi.org/10.1177/0272989X19893973>

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Change eval to TRUE if you want to knit this document.

```
rm(list = ls())      # clear memory (removes all the variables from the workspace)
```

01 Load packages

```
if (!require('pacman')) install.packages('pacman'); library(pacman) # use this package to conveniently
# load (install if required) packages from CRAN
p_load("dplyr", "tidyr", "reshape2", "devtools", "scales", "ellipse", "ggplot2", "lazyeval", "igraph",
# load (install if required) packages from GitHub
# install_github("DARTH-git/darthtools", force = TRUE) #Uncomment if there is a newer version
p_load_gh("DARTH-git/darthtools")
```

02 Load functions

```
# all functions are in the darthtools package
```

03 Model input

```
n_time_horizon_yr <- 60          # time horizon (in years)
cycle_length      <- 1          # cycle length in years (use 1/12 for monthly)
n_cycles          <- n_time_horizon_yr / cycle_length # number of cycles
v_names_cycles    <- paste("cycle", 0:n_cycles)      # cycle names
v_names_states    <- c("Healthy", "Sick", "Dead")    # state names
n_states          <- length(v_names_states)         # number of health states

### Discounting factors
d_c <- 0.03 # annual discount rate for costs
d_e <- 0.03 # annual discount rate for QALYs

### Strategies
v_names_str <- c("Standard of Care",          # store the strategy names
                "Treatment A",
                "Treatment B")
n_str       <- length(v_names_str)           # number of strategies

### Within-cycle correction (WCC) using Simpson's 1/3 rule
v_wcc <- gen_wcc(n_cycles = n_cycles, method = "Simpson1/3")

### Transition probabilities
p_HD_yr <- 0.01 # annual probability of dying when healthy
p_SD_yr <- 0.10 # annual probability of dying when sick
# Annual probability of becoming sick from Healthy, conditional on surviving cycle
p_HS_yr_SoC <- 0.05 # under standard of care
```

```

p_HS_yr_trtA <- 0.04 # under treatment A
p_HS_yr_trtB <- 0.02 # under treatment B

### State rewards

#### Costs
c_H_yr <- 400 # cost of one year in healthy state
c_S_yr <- 1000 # cost of one year in sick state
c_D_yr <- 0 # cost of one year in dead state
c_trtA_yr <- 800 # cost of treatment A (per year) in healthy state
c_trtB_yr <- 1500 # cost of treatment B (per year) in healthy state
#### Utilities
u_H <- 1 # utility when healthy
u_S <- 0.5 # utility when sick
u_D <- 0 # utility when dead

```

03.2 Calculate internal model parameters

```

### Cycle-specific discount weight for costs and effects
v_dwc <- 1 / ((1 + (d_e * cycle_length)) ^ (0:n_cycles))
v_dwe <- 1 / ((1 + (d_c * cycle_length)) ^ (0:n_cycles))

### Calculate cycle-specific transition probabilities
p_HD <- 1 - exp(-(-log(1 - p_HD_yr) * cycle_length)) # probability of dying from Healthy
p_SD <- 1 - exp(-(-log(1 - p_SD_yr) * cycle_length)) # probability of dying from Sick
# probability of becoming sick from Healthy
p_HS_SoC <- 1 - exp(-(-log(1 - p_HS_yr_SoC) * cycle_length)) # Standard of Care
p_HS_trtA <- 1 - exp(-(-log(1 - p_HS_yr_trtA) * cycle_length)) # Treatment A
p_HS_trtB <- 1 - exp(-(-log(1 - p_HS_yr_trtB) * cycle_length)) # Treatment B

### Calculate cycle-specific state rewards
#### Costs
v_c_SoC <- c(c_H_yr, c_S_yr, c_D_yr) * cycle_length # Standard of Care
v_c_trtA <- c(c_H_yr + c_trtA_yr, c_S_yr, c_D_yr) * cycle_length # Treatment A
v_c_trtB <- c(c_H_yr + c_trtB_yr, c_S_yr, c_D_yr) * cycle_length # Treatment B
#### QALYs
v_q_SoC <- c(u_H, u_S, u_D) * cycle_length # Standard of Care
v_q_trtA <- v_q_trtB <- v_q_SoC # Treatments A and B have same utilities as SoC

```

04 Construct state-transition models

```

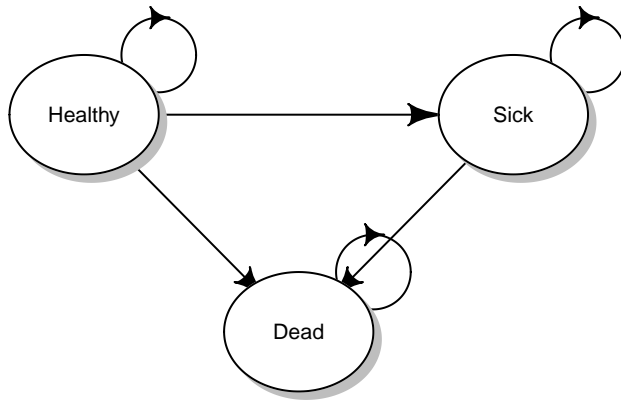
m_P_diag <- matrix(0, nrow = n_states, ncol = n_states, dimnames = list(v_names_states, v_names_states))
m_P_diag["Healthy", "Sick"] = ""
m_P_diag["Healthy", "Dead"] = ""
m_P_diag["Healthy", "Healthy"] = ""
m_P_diag["Sick", "Dead"] = ""
m_P_diag["Sick", "Sick"] = ""

```

```

m_P_diag["Dead" , "Dead" ] = ""
layout.fig <- c(2, 1)
plotmat(t(m_P_diag), t(layout.fig), self.cex = 0.5, curve = 0, arr.pos = 0.8,
        latex = T, arr.type = "curved", relsize = 0.85, box.prop = 0.8,
        cex = 0.8, box.cex = 0.7, lwd = 1)

```



04.1 Initial state vector

```

# All starting healthy
v_m_init <- c("Healthy" = 1, "Sick" = 0, "Dead" = 0)
v_m_init

```

```

## Healthy    Sick    Dead
##          1      0      0

```

04.2 Initialize cohort traces

```

### Initialize cohort trace for SoC
m_M_SoC <- matrix(0,
                  nrow = (n_cycles + 1), ncol = n_states,
                  dimnames = list(v_names_cycles, v_names_states))
# Store the initial state vector in the first row of the cohort trace
m_M_SoC[1, ] <- v_m_init

## Initialize cohort traces for treatments A and B
# Structure and initial states are the same as for SoC
m_M_trtA <- m_M_trtB <- m_M_SoC

```

04.3 Create transition probability arrays

```

## Create transition probability matrices for strategy SoC
### Initialize transition probability matrix
# All transitions to a non-death state are assumed to be conditional on survival

```

```

m_P_SoC <- matrix(0,
                  nrow = n_states, ncol = n_states,
                  dimnames = list(v_names_states, v_names_states))
### Fill in matrix
# from Healthy
m_P_SoC["Healthy", "Healthy"] <- (1 - p_HD) * (1 - p_HS_SoC)
m_P_SoC["Healthy", "Sick"] <- (1 - p_HD) * p_HS_SoC
m_P_SoC["Healthy", "Dead"] <- p_HD
# from Sick
m_P_SoC["Sick", "Sick"] <- 1 - p_SD
m_P_SoC["Sick", "Dead"] <- p_SD
# from Dead
m_P_SoC["Dead", "Dead"] <- 1

## Treatment A
# Start with same matrix as SoC, but replace parameters that differ for trtA
m_P_trtA <- m_P_SoC
m_P_trtA["Healthy", "Healthy"] <- (1 - p_HD) * (1 - p_HS_trtA)
m_P_trtA["Healthy", "Sick"] <- (1 - p_HD) * p_HS_trtA

## Treatment B
# Start with same matrix as SoC, but replace parameters that differ for trtB
m_P_trtB <- m_P_SoC
m_P_trtB["Healthy", "Healthy"] <- (1 - p_HD) * (1 - p_HS_trtB)
m_P_trtB["Healthy", "Sick"] <- (1 - p_HD) * p_HS_trtB

## Check if transition probability matrices are valid
### Check that transition probabilities are in [0, 1]
check_transition_probability(m_P_SoC, verbose = TRUE)

## [1] "Valid transition probabilities"

check_transition_probability(m_P_trtA, verbose = TRUE)

## [1] "Valid transition probabilities"

check_transition_probability(m_P_trtB, verbose = TRUE)

## [1] "Valid transition probabilities"

### Check that all rows sum to 1
check_sum_of_transition_array(m_P_SoC, n_states = n_states, n_cycles = n_cycles, verbose = TRUE)

## [1] "This is a valid transition matrix"

check_sum_of_transition_array(m_P_trtA, n_states = n_states, n_cycles = n_cycles, verbose = TRUE)

## [1] "This is a valid transition matrix"

```

```
check_sum_of_transition_array(m_P_trtB, n_states = n_states, n_cycles = n_cycles, verbose = TRUE)
```

```
## [1] "This is a valid transition matrix"
```

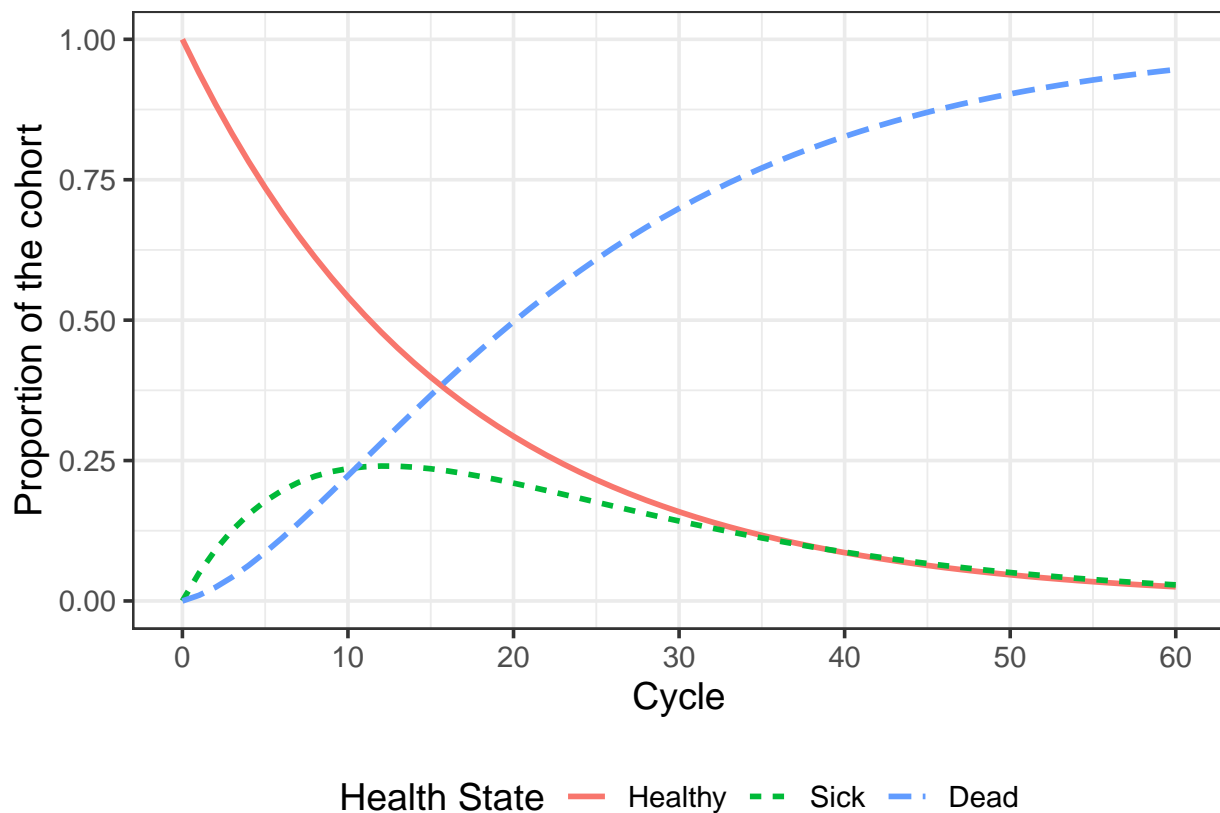
05 Run cohort state transition model

```
## Loop over time
# Calculating cohort state based on previous state and transition matrix
for (t in 1:n_cycles){
  # For SoC
  m_M_SoC[t + 1, ] <- m_M_SoC[t, ] %*% m_P_SoC
  # For treatment A
  m_M_trtA[t + 1, ] <- m_M_trtA[t, ] %*% m_P_trtA
  # For treatment B
  m_M_trtB[t + 1, ] <- m_M_trtB[t, ] %*% m_P_trtB
}
```

06 Plot Outputs

06.1 Plot the cohort trace for strategies SoC

```
plot_trace(m_M_SoC)
```



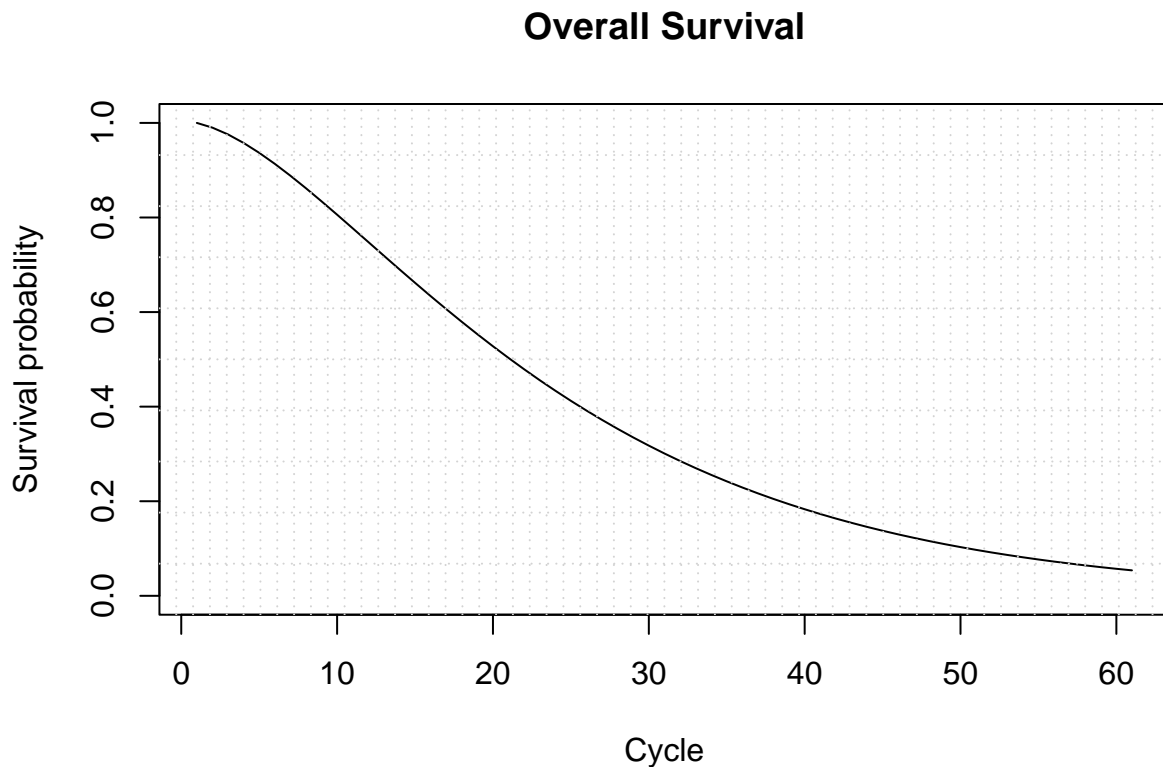
06.2 Overall Survival (OS)

Print the overall survival for the Standard of Care

```
v_os_SoC <- 1 - m_M_SoC[, "Dead"]      # calculate the overall survival (OS) probability
v_os_SoC <- rowSums(m_M_SoC[, 1:2])    # alternative way of calculating the OS probability

plot(v_os_SoC, type = 'l',
     ylim = c(0, 1),
     ylab = "Survival probability",
     xlab = "Cycle",
     main = "Overall Survival") # create a simple plot showing the OS

# add grid
grid(nx = n_cycles, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"),
     equilogs = TRUE)
```



06.2.1 Life Expectancy (LE)

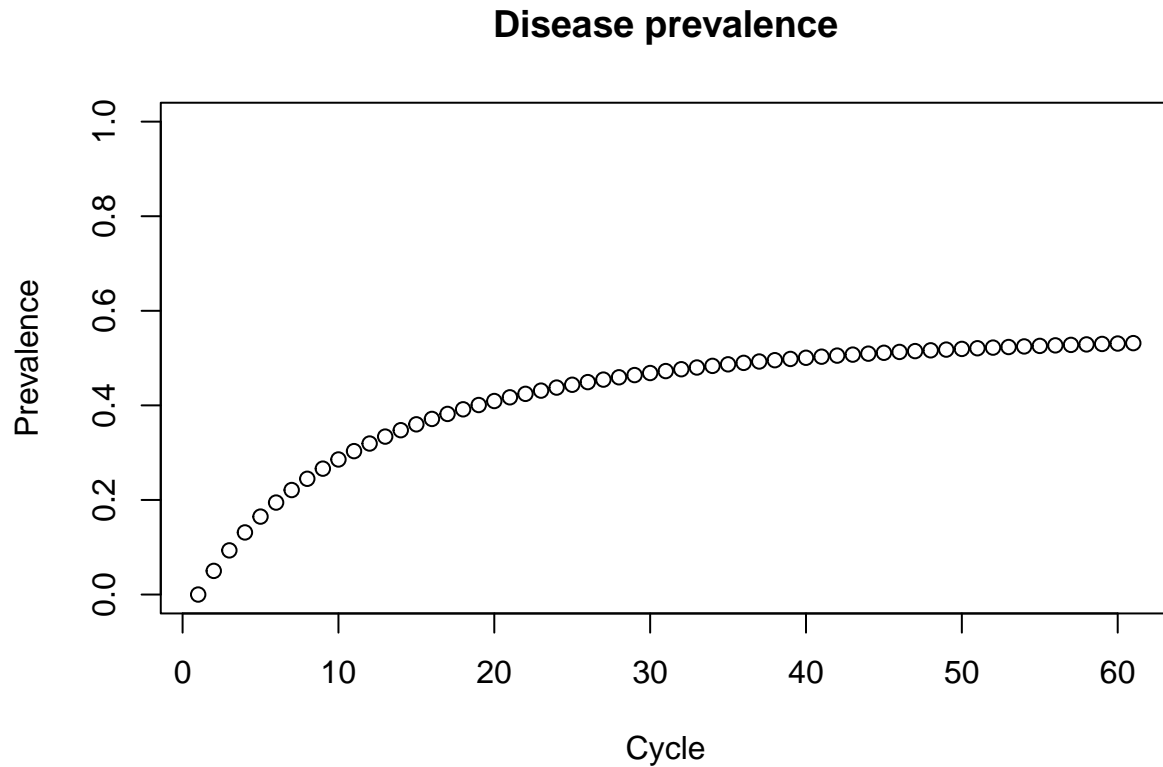
```
le_SoC <- sum(v_os_SoC) # summing probability of OS over time (i.e. life expectancy)
```

06.2.2 Disease prevalence


```

v_prev <- m_M_SoC[, "Sick"]/v_os_SoC
plot(v_prev,
     ylim = c(0, 1),
     ylab = "Prevalence",
     xlab = "Cycle",
     main = "Disease prevalence")

```



07 State Rewards

```

## Scale by the cycle length
# Vector of state utilities under strategy SoC
v_u_SoC    <- c(H = u_H,
               S = u_S,
               D = u_D) * cycle_length
# Vector of state costs under strategy SoC
v_c_SoC    <- c(H = c_H_yr,
               S = c_S_yr,
               D = c_D_yr) * cycle_length
# Vector of state utilities under treatment A
v_u_trtA   <- c(H = u_H,
               S = u_S,
               D = u_D) * cycle_length
# Vector of state costs under treatment A
v_c_trtA   <- c(H = c_H_yr + c_trtA_yr,
               S = c_S_yr,
               D = c_D_yr) * cycle_length

```

```

# Vector of state utilities under treatment B
v_u_trtB <- c(H = u_H,
              S = u_S,
              D = u_D) * cycle_length
# Vector of state costs under treatment B
v_c_trtB <- c(H = c_H_yr + c_trtB_yr,
              S = c_S_yr,
              D = c_D_yr) * cycle_length

## Store state rewards
# Store the vectors of state utilities for each strategy in a list
l_u <- list(SQ = v_u_SoC,
            A = v_u_trtA,
            B = v_u_trtB)
# Store the vectors of state cost for each strategy in a list
l_c <- list(SQ = v_c_SoC,
            A = v_c_trtA,
            B = v_c_trtB)

# assign strategy names to matching items in the lists
names(l_u) <- names(l_c) <- v_names_str

```

08 Compute expected outcomes

```

# Create empty vectors to store total costs and QALYs
v_tot_cost <- v_tot_qaly <- vector(mode = "numeric", length = n_str)
names(v_tot_qaly) <- names(v_tot_cost) <- v_names_str

### Expected discounted cost for each strategy
v_tot_cost["Standard of Care"] <- t(m_M_SoC %*% v_c_SoC) %*% (v_dwe * v_wcc)
v_tot_cost["Treatment A"] <- t(m_M_trtA %*% v_c_trtA) %*% (v_dwe * v_wcc)
v_tot_cost["Treatment B"] <- t(m_M_trtB %*% v_c_trtB) %*% (v_dwe * v_wcc)

### Expected discounted QALYs for each strategy
v_tot_qaly["Standard of Care"] <- t(m_M_SoC %*% v_q_SoC) %*% (v_dwe * v_wcc)
v_tot_qaly["Treatment A"] <- t(m_M_trtA %*% v_q_trtA) %*% (v_dwe * v_wcc)
v_tot_qaly["Treatment B"] <- t(m_M_trtB %*% v_q_trtB) %*% (v_dwe * v_wcc)

```

09 Cost-effectiveness analysis (CEA)

```

## Incremental cost-effectiveness ratios (ICERs)
df_cea <- calculate_icers(cost = v_tot_cost,
                          effect = v_tot_qaly,
                          strategies = v_names_str)

df_cea

```

##	Strategy	Cost	Effect	Inc_Cost	Inc_Effect
----	----------	------	--------	----------	------------

```
## Standard of Care Standard of Care 8574.738 12.79462 NA NA
## Treatment B Treatment B 32745.314 17.16887 24170.58 4.374253
## Treatment A Treatment A 18272.100 13.94028 NA NA
##
## ICER Status
## Standard of Care NA ND
## Treatment B 5525.647 ND
## Treatment A NA ED
```

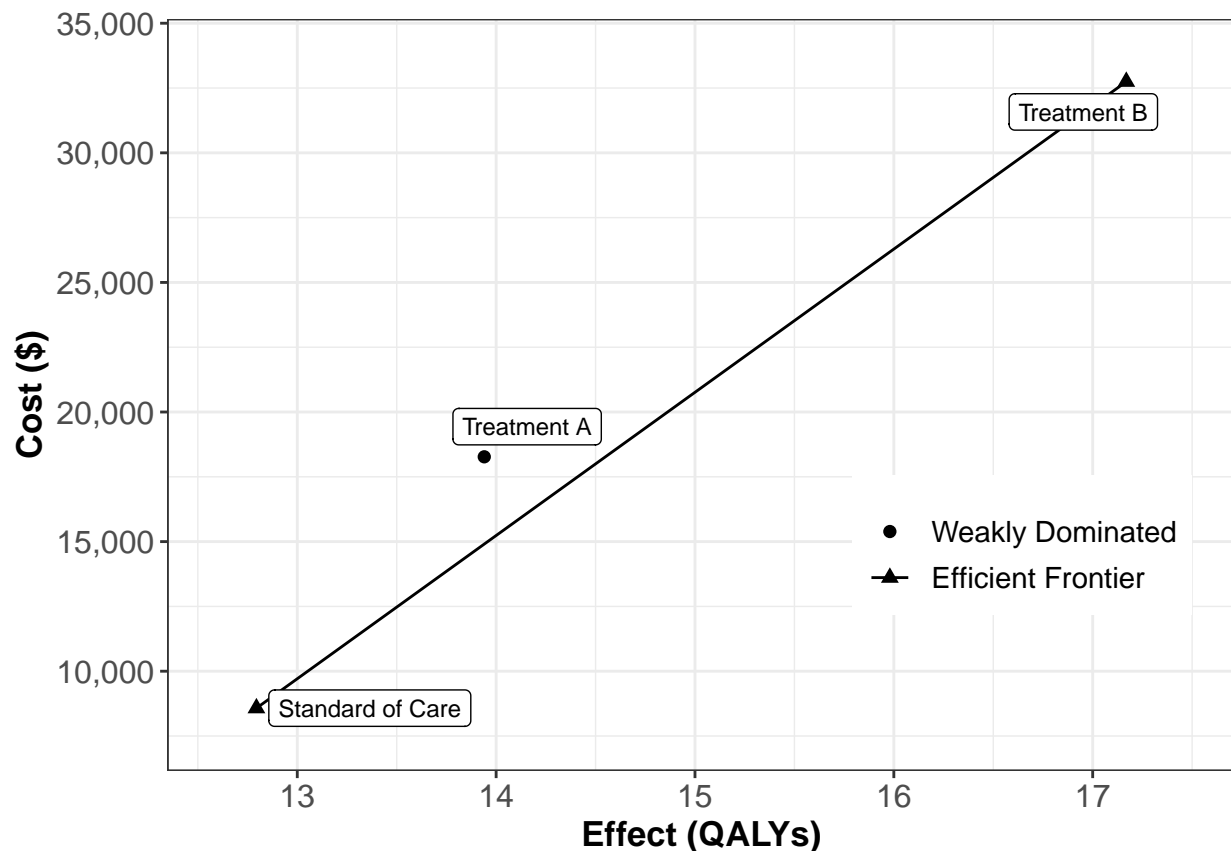
CEA table in proper format

```
table_cea <- format_table_cea(df_cea)
table_cea
```

```
##
## Strategy Costs ($) QALYs Incremental Costs ($)
## Standard of Care Standard of Care 8,575 12.79 <NA>
## Treatment B Treatment B 32,745 17.17 24,171
## Treatment A Treatment A 18,272 13.94 <NA>
##
## Incremental QALYs ICER ($/QALY) Status
## Standard of Care NA <NA> ND
## Treatment B 4.37 5,526 ND
## Treatment A NA <NA> ED
```

CEA frontier

```
plot(df_cea, label = "all", txtsize = 14) +
  expand_limits(x = max(table_cea$QALYs) + 0.1) +
  theme(legend.position = c(0.8, 0.3))
```



10 Deterministic Sensitivity Analysis (DSA)

```
## Load model, CEA and PSA functions
source('Functions_cSTM_3state.R')
```

10.1 Model input for SA

```
l_params_all <- list(
  # Transition probabilities
  # probability of dying
  p_HD_yr      = 0.01, # annual probability of dying when healthy
  p_SD_yr      = 0.10, # annual probability of dying when sick
  # Annual probability of becoming sick from Healthy, conditional on surviving cycle
  p_HS_yr_SoC  = 0.05, # under standard of care
  p_HS_yr_trtA = 0.04, # under treatment A
  p_HS_yr_trtB = 0.02, # under treatment B

  ### State rewards

  #### Costs
  c_H_yr      = 400, # cost of one year in healthy state
  c_S_yr      = 1000, # cost of one year in sick state
  c_D_yr      = 0, # cost of one year in dead state
  c_trtA_yr   = 800, # cost of treatment A (per year) in healthy state
  c_trtB_yr   = 1500, # cost of treatment B (per year) in healthy state
  #### Utilities
  u_H         = 1, # utility when healthy
  u_S         = 0.5, # utility when sick
  u_D         = 0, # utility when dead
  # Discount rates
  d_e         = 0.03, # discount rate per cycle equal discount of costs and QALYs by 3%
  d_c         = 0.03, # discount rate per cycle equal discount of costs and QALYs by 3%
  # Time horizon
  n_time_horizon_yr = 60, # time horizon (in years)
  cycle_length      = 1, # cycle length in years (use 1/12 for monthly)
)
```

Test model functions

A function is defined in the `Functions_markov_3state_time.R` file. The first is the `calculate_ce_out()` function which runs the decision model and uses the resulting Markov trace to compute the total costs, QALYs, and net monetary benefit (NMB) for each strategy, returning a data frame of costs and QALYs.

```
# Try the calculate_ce_out() function
df_ce <- calculate_ce_out(l_params_all)
```

```
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
```

```
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
```

```
df_ce
```

```
##               Strategy      Cost   Effect      NMB
## Standard of Care Standard of Care 8574.738 12.79462 119371.4
## Treatment A      Treatment A 18272.100 13.94028 121130.7
## Treatment B      Treatment B 32745.314 17.16887 138943.4
```

```
# Get strategies names (will be used to label plots)
v_names_str <- df_ce$Strategy
n_str <- length(v_names_str)
```

10.2 One-way sensitivity analysis (OWSA)

```
options(scipen = 999) # disabling scientific notation in R
# dataframe containing all parameters, their base case values, and the min and
# max values of the parameters of interest
df_params_owsa <- data.frame(pars = c("c_trtA_yr", "c_trtB_yr", "c_S_yr"),
                             min = c(300, 500, 500), # min parameter values
                             max = c(1200, 2000, 2000) # max parameter values
                             )
owsa_nmb <- run_owsa_det(params_range = df_params_owsa, # dataframe with parameters for OWSA
                        params_basecase = l_params_all, # list with all parameters
                        nsamp = 100, # number of parameter values
                        FUN = calculate_ce_out, # function to compute outputs
                        outcomes = c("NMB"), # output to do the OWSA on
                        strategies = v_names_str, # names of the strategies
                        n_wtp = 5000) # extra argument to pass to FUN
```

```
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
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## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
## |
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
```

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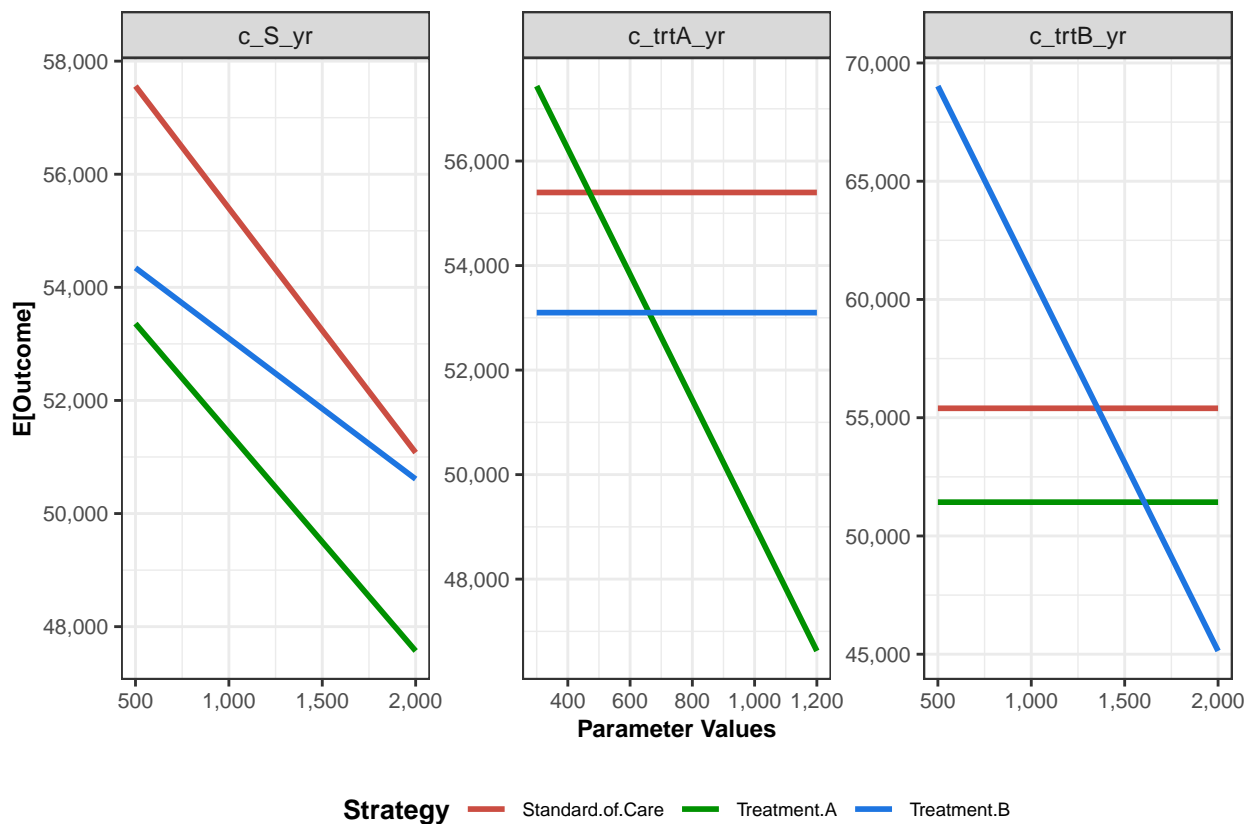
=====

=====

=====

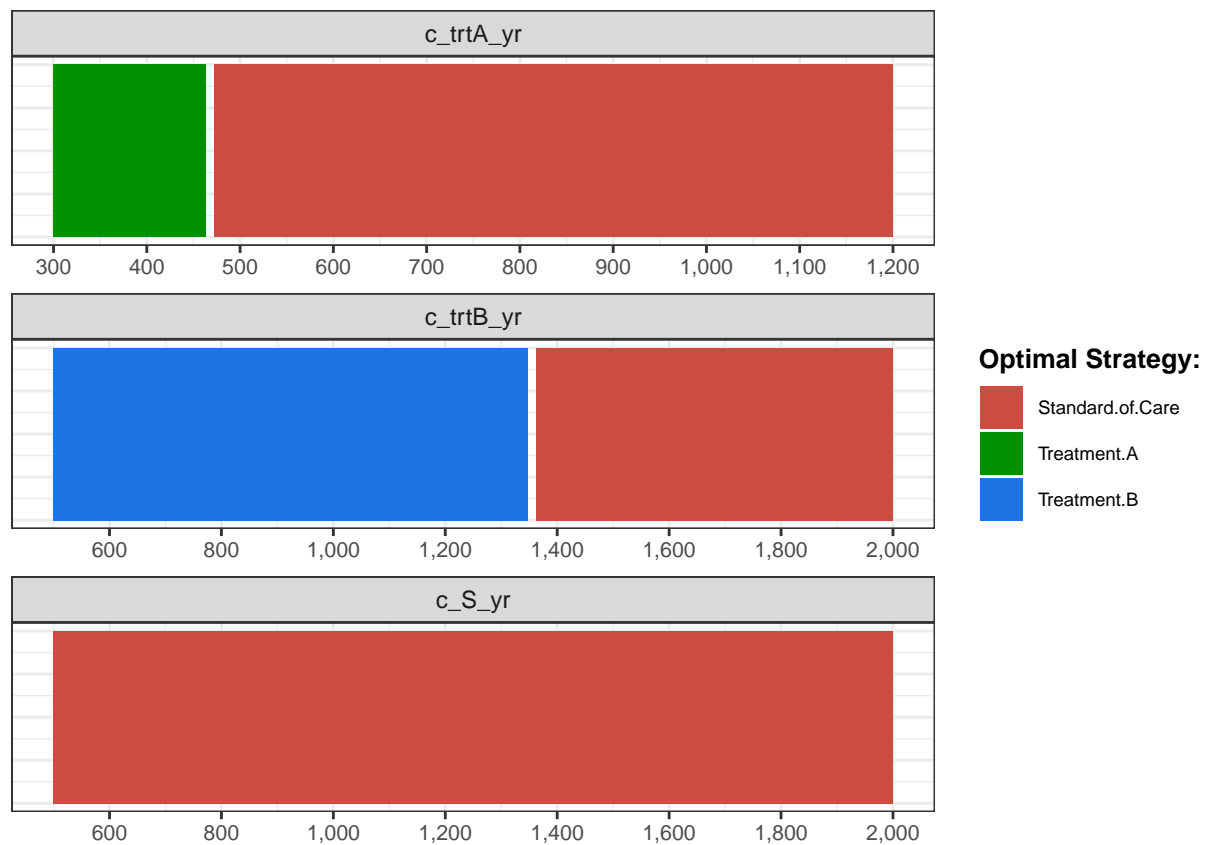
```
## |
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
## [1] "This is a valid transition matrix"
```

```
plot(owsa_nmb, txtsize = 10, n_x_ticks = 4,
     facet_scales = "free") +
  theme(legend.position = "bottom")
```



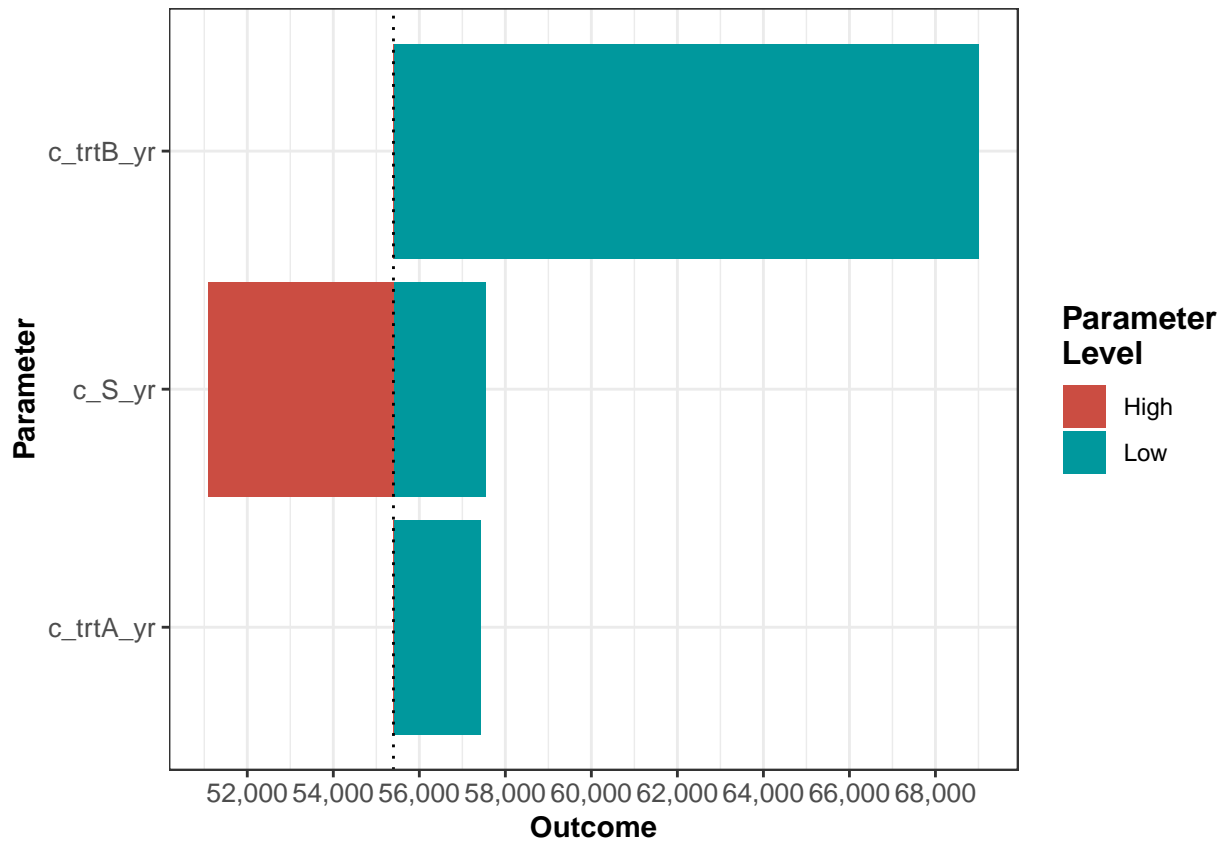
10.2.1 Optimal strategy with OWSA

```
owsa_opt_strat(owsa = owsa_nmb, txtsize = 10)
```



10.2.2 Tornado plot

```
owsa_tornado(owsa = owsa_nmb)
```

10.3 Two-way sensitivity analysis (TWSA)

```
# dataframe containing all parameters, their basecase values, and the min and
# max values of the parameters of interest
df_params_twsa <- data.frame(pars = c("c_trtA_yr", "c_trtB_yr"),
                             min  = c(300, 500), # min parameter values
                             max  = c(1200, 2000) # max parameter values
                             )

twsa_nmb <- run_twsa_det(params_range = df_params_twsa, # dataframe with parameters for TWSA
                        params_basecase = l_params_all, # list with all parameters
                        nsamp = 40, # number of parameter values
                        FUN = calculate_ce_out, # function to compute outputs
                        outcomes = "NMB", # output to do the TWSA on
                        strategies = v_names_str, # names of the strategies
                        n_wtp = 5000) # extra argument to pass to FUN

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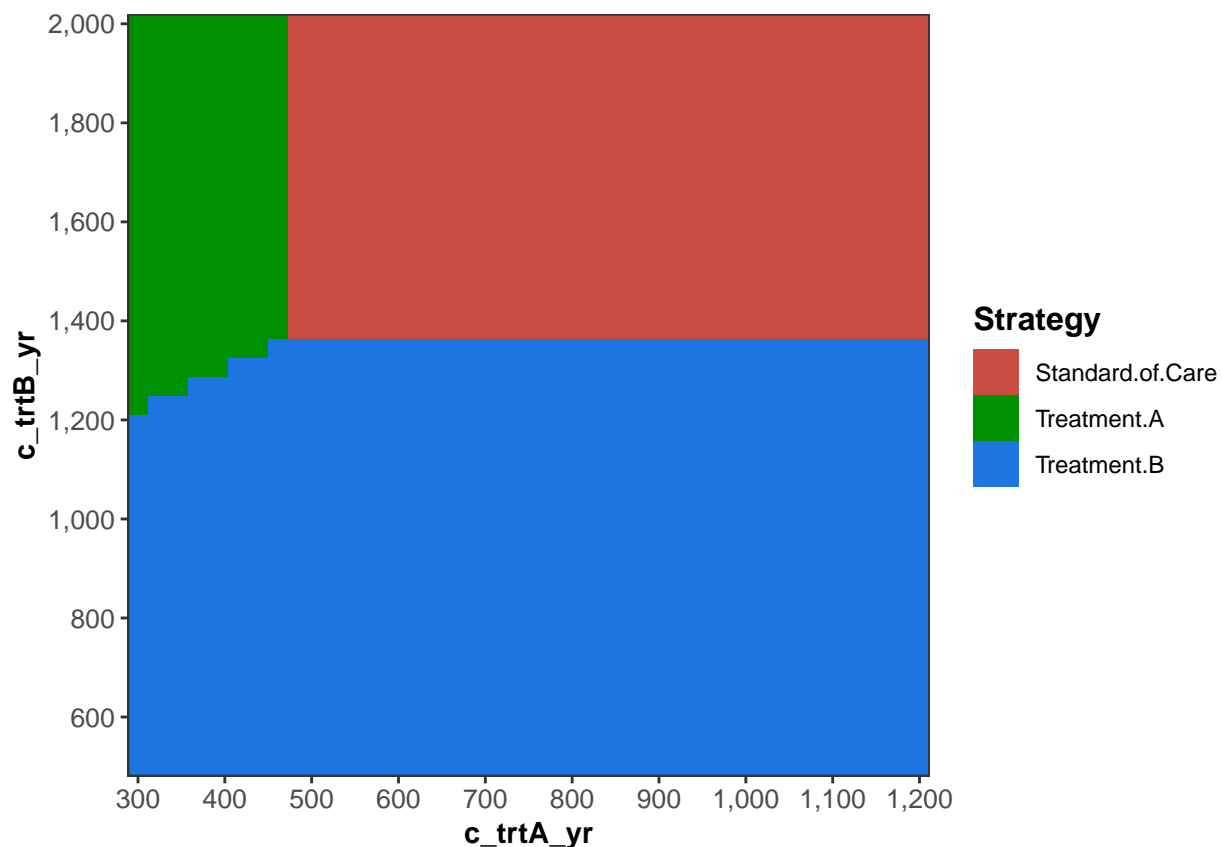
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```

10.3.1 Plot TWSA

```
plot(twsa_nmb)
```



11 Probabilistic Sensitivity Analysis (PSA)

11.1 Model input

```
# Store the parameter names into a vector
v_names_params <- names(l_params_all)

## Test functions to generate CE outcomes and PSA dataset
# Test function to compute CE outcomes
calculate_ce_out(l_params_all)

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##
##           Strategy      Cost    Effect    NMB
## Standard of Care Standard of Care 8574.738 12.79462 119371.4
## Treatment A      Treatment A 18272.100 13.94028 121130.7
## Treatment B      Treatment B 32745.314 17.16887 138943.4
```

```
# Test function to generate PSA input dataset
generate_psa_params(10)
```

```
##           p_HD_yr    p_SD_yr p_HS_yr_SoC p_HS_yr_trtA p_HS_yr_trtB    c_H_yr
## 1  0.0008905932 0.07962620 0.04080578 0.07084322 0.01716266 390.7068
## 2  0.0092979184 0.14336539 0.06172540 0.05135318 0.02601948 393.7788
## 3  0.0069371243 0.08285488 0.04973326 0.03317056 0.01537997 388.4159
## 4  0.0148746692 0.12408528 0.03997063 0.04320045 0.01843236 348.6654
## 5  0.0008164595 0.09565414 0.07481755 0.05311687 0.01753576 383.0443
## 6  0.0144162389 0.13613101 0.03950458 0.03384405 0.01839549 337.9317
## 7  0.0291361361 0.10579557 0.05236064 0.01984253 0.02530839 375.8565
## 8  0.0072422302 0.06572414 0.04388866 0.07142634 0.01843345 443.4329
## 9  0.0173178373 0.12304579 0.04945120 0.04120239 0.02108065 265.5241
## 10 0.0038339205 0.12801141 0.04737147 0.03291192 0.02603099 474.4756
##           c_S_yr c_D c_trtA_yr c_trtB_yr u_H      u_S u_D
## 1  984.6521    0      800      1500    1 0.5399242    0
## 2  820.5960    0      800      1500    1 0.5418116    0
## 3  1138.0161   0      800      1500    1 0.5599530    0
## 4  858.9336    0      800      1500    1 0.5384445    0
## 5  1066.2746   0      800      1500    1 0.5669157    0
## 6  1056.6110   0      800      1500    1 0.5479511    0
## 7  1061.5311   0      800      1500    1 0.4594113    0
## 8  1193.5129   0      800      1500    1 0.4863897    0
## 9   800.1153   0      800      1500    1 0.5303334    0
## 10 958.2335    0      800      1500    1 0.5053532    0
```

```
## Generate PSA dataset
# Number of simulations
n_sim <- 1000

# Generate PSA input dataset
df_psa_input <- generate_psa_params(n_sim = n_sim)
# First six observations
head(df_psa_input)
```

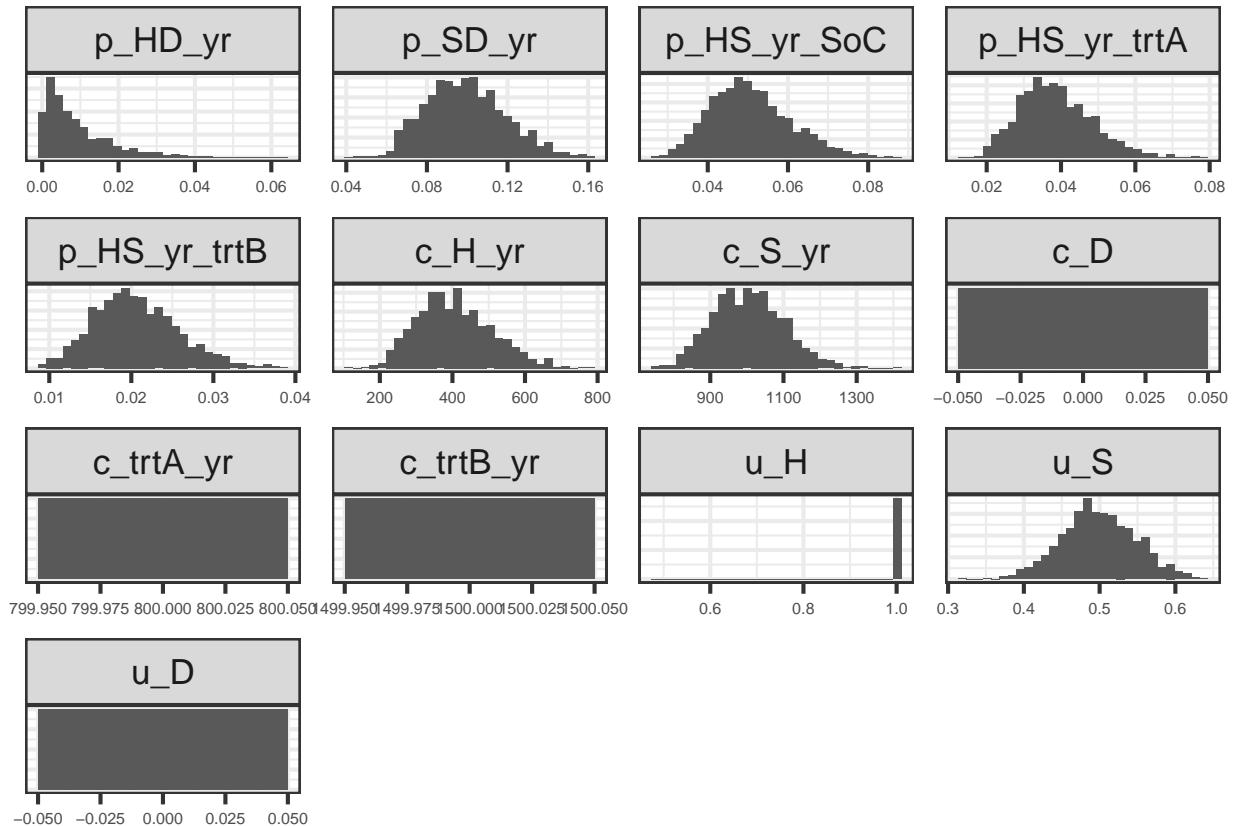
```
##           p_HD_yr    p_SD_yr p_HS_yr_SoC p_HS_yr_trtA p_HS_yr_trtB    c_H_yr
## 1 0.0008905932 0.08345302 0.03639243 0.04625157 0.02373915 378.9834
## 2 0.0092979184 0.08705903 0.04863376 0.03545299 0.02365531 250.9753
## 3 0.0069371243 0.09384916 0.04795652 0.03519947 0.01376117 334.8414
## 4 0.0148746692 0.09837925 0.03701927 0.04145198 0.01629833 403.5015
## 5 0.0008164595 0.10916526 0.05795409 0.03383705 0.02144999 659.2460
## 6 0.0144162389 0.14199407 0.05426025 0.02987467 0.01303275 509.8460
##           c_S_yr c_D c_trtA_yr c_trtB_yr u_H      u_S u_D
## 1 1133.2735    0      800      1500    1 0.4303221    0
## 2 1146.5301    0      800      1500    1 0.4839519    0
## 3 1208.4904    0      800      1500    1 0.5465168    0
## 4 1113.9417    0      800      1500    1 0.5177278    0
## 5  980.0201    0      800      1500    1 0.4314829    0
## 6 1017.4345    0      800      1500    1 0.4754447    0
```

```
### Histogram of parameters
ggplot(melt(df_psa_input, variable.name = "Parameter"), aes(x = value)) +
```

```

facet_wrap(~Parameter, scales = "free") +
geom_histogram(aes(y = ..density..)) +
ylab("") +
theme_bw(base_size = 16) +
theme(axis.text = element_text(size = 6),
      axis.title.x = element_blank(),
      axis.title.y = element_blank(),
      axis.text.y = element_blank(),
      axis.ticks.y = element_blank())

```



11.2 Run PSA

```

# Initialize data.frames with PSA output
# data.frame of costs
df_c <- as.data.frame(matrix(0,
                             nrow = n_sim,
                             ncol = n_str))

colnames(df_c) <- v_names_str
# data.frame of effectiveness
df_e <- as.data.frame(matrix(0,
                             nrow = n_sim,
                             ncol = n_str))

colnames(df_e) <- v_names_str

```

```

# Conduct probabilistic sensitivity analysis
# Run Markov model on each parameter set of PSA input dataset
n_time_init_psa_series <- Sys.time()
for (i in 1:n_sim) { # i <- 1
  l_psa_input <- update_param_list(l_params_all, df_psa_input[i,])
  # Outcomes
  l_out_ce_temp <- calculate_ce_out(l_psa_input)
  df_c[i, ] <- l_out_ce_temp$Cost
  df_e[i, ] <- l_out_ce_temp$Effect
  # Display simulation progress
  if (i/(n_sim/100) == round(i/(n_sim/100), 0)) { # display progress every 5%
    cat('\r', paste(i/n_sim * 100, "% done", sep = " "))
  }
}

```

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##    34 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
## [1] "This is a valid transition matrix"  
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## [1] "Valid transition probabilities"  
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## 43 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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## 44 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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## 46 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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##   52 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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##   55 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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##   61 % done[1] "Valid transition probabilities"  
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## 62 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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##   64 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
## [1] "This is a valid transition matrix"  
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##    70 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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## 79 % done[1] "Valid transition probabilities"  
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##   80 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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##   88 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
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## 91 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"  
## [1] "This is a valid transition matrix"  
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##   97 % done[1] "Valid transition probabilities"  
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## [1] "Valid transition probabilities"
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## 100 % done
```

```
n_time_end_psa_series <- Sys.time()
n_time_total_psa_series <- n_time_end_psa_series - n_time_init_psa_series
print(paste0("PSA with ", scales::comma(n_sim), " simulations run in series in ",
            round(n_time_total_psa_series, 2), " ",
            units(n_time_total_psa_series)))
```

```
## [1] "PSA with 1,000 simulations run in series in 1.5 secs"
```

11.3 Visualize PSA results for CEA

```
### Create PSA object
l_psa <- make_psa_obj(cost      = df_c,
                     effectiveness = df_e,
                     parameters  = df_psa_input,
                     strategies   = v_names_str)
l_psa$strategies <- v_names_str
colnames(l_psa$effectiveness) <- v_names_str
colnames(l_psa$cost) <- v_names_str

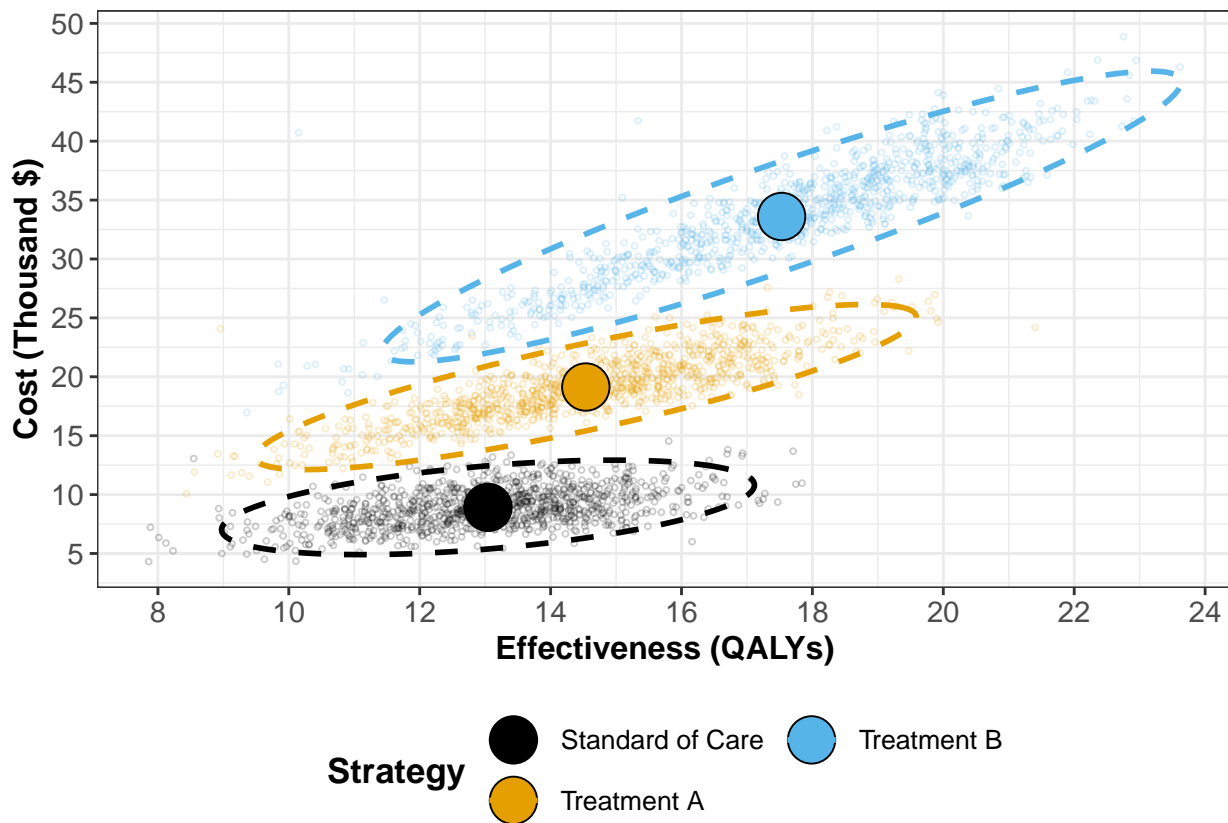
# Vector with willingness-to-pay (WTP) thresholds.
v_wtp <- seq(0, 30000, by = 1000)
```

11.3.1 Cost-Effectiveness Scatter plot

```

### Cost-Effectiveness Scatter plot
txtsize <- 13
gg_scattter <- plot_psa(l_psa, txtsize = txtsize) +
  ggthemes::scale_color_colorblind() +
  ggthemes::scale_fill_colorblind() +
  scale_y_continuous("Cost (Thousand $)",
    breaks = number_ticks(10),
    labels = function(x) x/1000) +
  xlab("Effectiveness (QALYs)") +
  guides(col = guide_legend(nrow = 2)) +
  theme(legend.position = "bottom")
gg_scattter

```



11.3.2 Incremental cost-effectiveness ratios (ICERs) with probabilistic output

```

### Incremental cost-effectiveness ratios (ICERs) with probabilistic output
# Compute expected costs and effects for each strategy from the PSA
df_out_ce_psa <- summary(l_psa)
df_cea_psa <- calculate_icers(cost      = df_out_ce_psa$meanCost,
                             effect    = df_out_ce_psa$meanEffect,
                             strategies = df_out_ce_psa$Strategy)
df_cea_psa

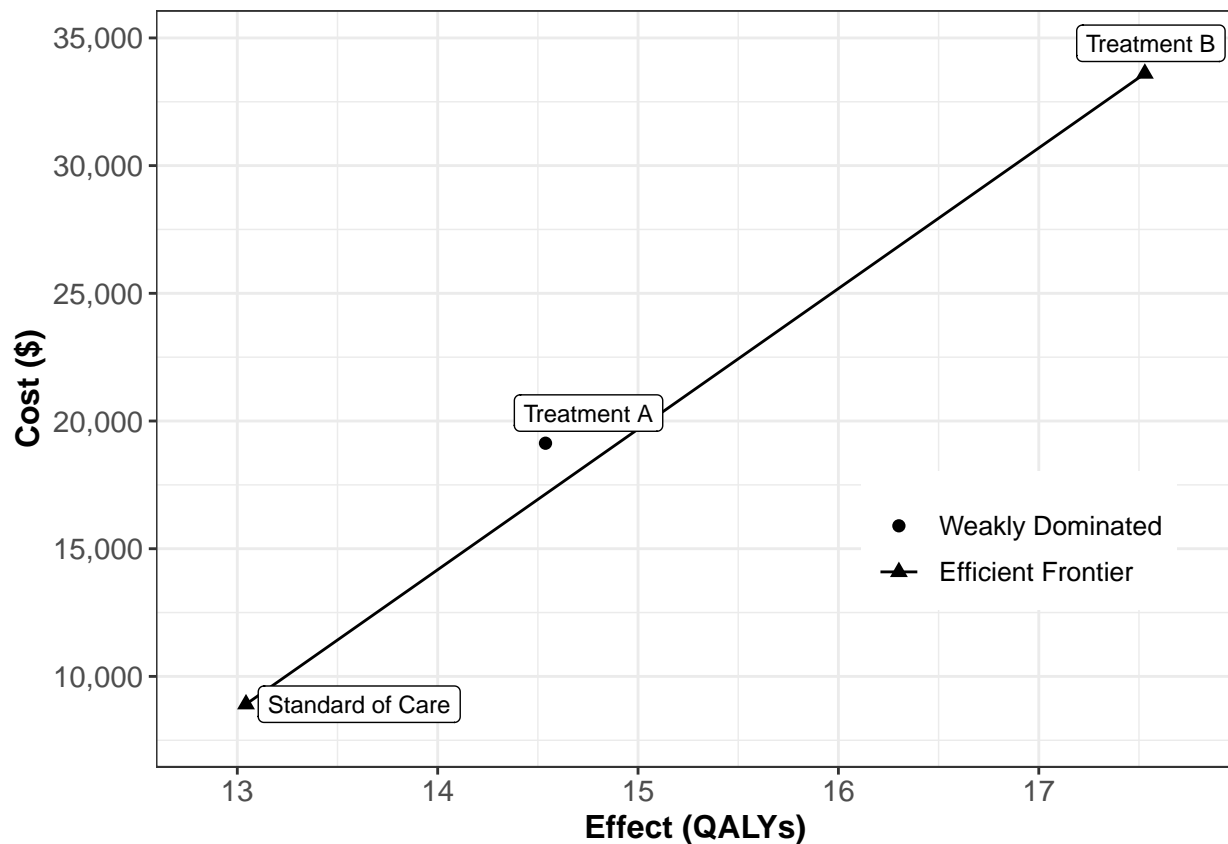
```

##	Strategy	Cost	Effect	Inc_Cost	Inc_Effect	ICER	Status
----	----------	------	--------	----------	------------	------	--------

## 1	Standard of Care	8911.866	13.04343	NA	NA	NA	ND
## 2	Treatment B	33605.757	17.52934	24693.89	4.485904	5504.775	ND
## 3	Treatment A	19130.458	14.53810	NA	NA	NA	ED

11.3.3 Plot cost-effectiveness frontier with probabilistic output

```
### Plot cost-effectiveness frontier with probabilistic output
plot_icers(df_cea_psa, label = "all", txtsize = txtsize) +
  expand_limits(x = max(table_cea$QALYs) + 0.1) +
  theme(legend.position = c(0.8, 0.3))
```

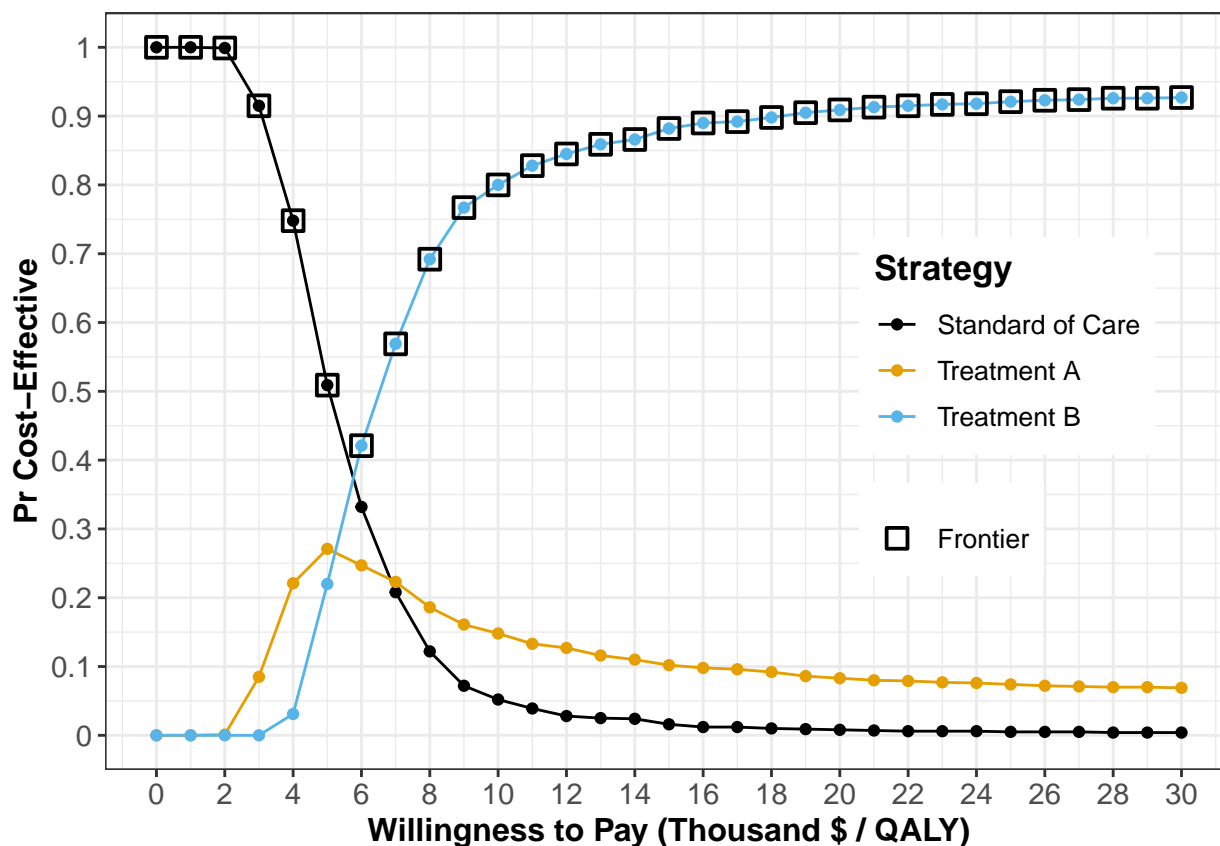


11.3.4 Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)

```
### Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)
ceac_obj <- ceac(wtp = v_wtp, psa = l_psa)
# Regions of highest probability of cost-effectiveness for each strategy
summary(ceac_obj)
```

##	range_min	range_max	cost_eff_strat
## 1	0	6000	Standard of Care
## 2	6000	30000	Treatment B


```
# CEAC & CEAF plot
gg_ceac <- plot_ceac(ceac_obj, txtsize = txtsize, xlim = c(0, NA), n_x_ticks = 14) +
  ggthemes::scale_color_colorblind() +
  ggthemes::scale_fill_colorblind() +
  theme(legend.position = c(0.8, 0.48))
gg_ceac
```



11.3.5 Expected Loss Curves (ELCs)

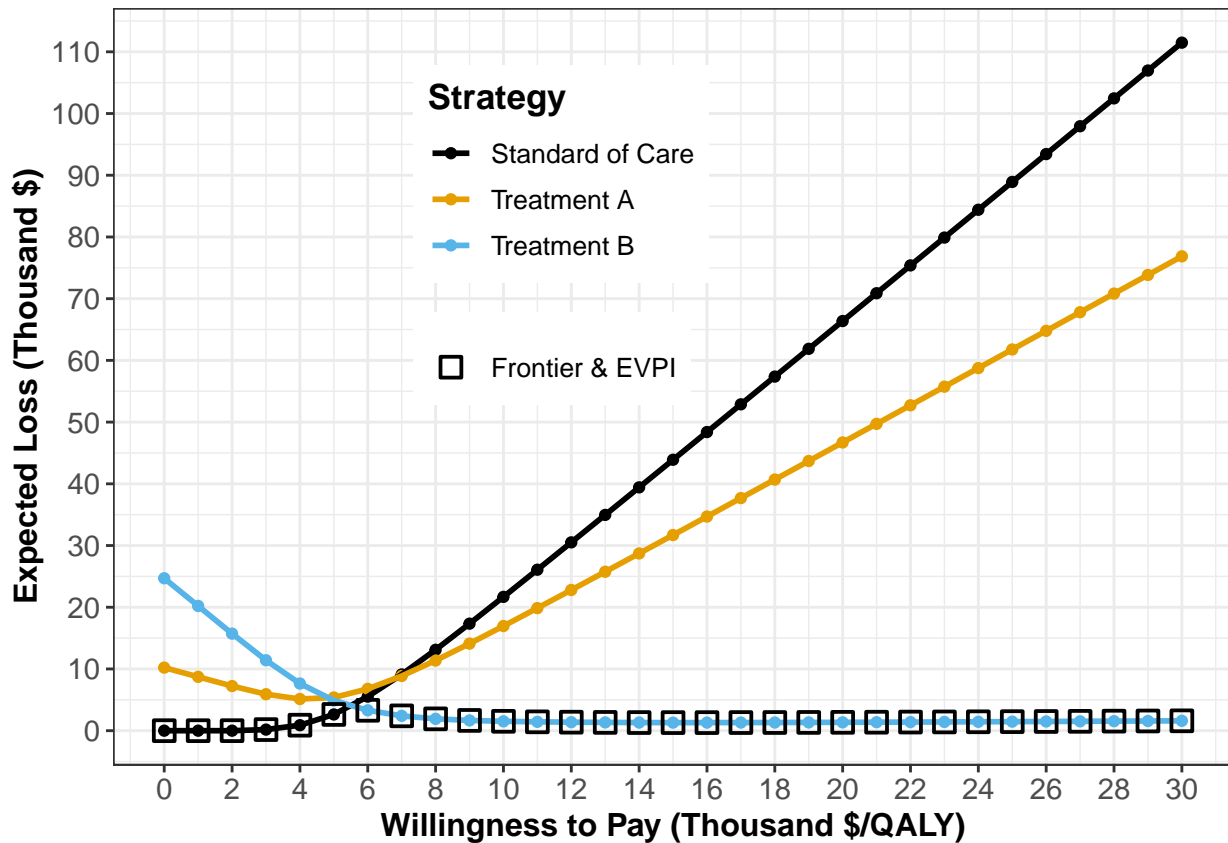
```
### Expected Loss Curves (ELCs)
elc_obj <- calc_exp_loss(wtp = v_wtp, psa = l_psa)
elc_obj
```

##	WTP	Strategy	Expected_Loss	On_Frontier
## 1	0	Standard of Care	0.0000000	TRUE
## 2	0	Treatment A	10218.5921641	FALSE
## 3	0	Treatment B	24693.8911337	FALSE
## 4	1000	Standard of Care	0.0000000	TRUE
## 5	1000	Treatment A	8723.9262523	FALSE
## 6	1000	Treatment B	20207.9869616	FALSE
## 7	2000	Standard of Care	0.1134618	TRUE
## 8	2000	Treatment A	7229.3738023	FALSE
## 9	2000	Treatment B	15722.1962513	FALSE

## 10	3000	Standard of Care	174.6768998	TRUE
## 11	3000	Treatment A	5909.2713285	FALSE
## 12	3000	Treatment B	11410.8555172	FALSE
## 13	4000	Standard of Care	888.0796150	TRUE
## 14	4000	Treatment A	5128.0081319	FALSE
## 15	4000	Treatment B	7638.3540603	FALSE
## 16	5000	Standard of Care	2628.9453150	TRUE
## 17	5000	Treatment A	5374.2079200	FALSE
## 18	5000	Treatment B	4893.3155881	FALSE
## 19	6000	Standard of Care	5523.4819378	FALSE
## 20	6000	Treatment A	6774.0786311	FALSE
## 21	6000	Treatment B	3301.9480388	TRUE
## 22	7000	Standard of Care	9108.5898570	FALSE
## 23	7000	Treatment A	8864.5206385	FALSE
## 24	7000	Treatment B	2401.1517859	TRUE
## 25	8000	Standard of Care	13107.7888494	FALSE
## 26	8000	Treatment A	11369.0537191	FALSE
## 27	8000	Treatment B	1914.4466062	TRUE
## 28	9000	Standard of Care	17341.8213452	FALSE
## 29	9000	Treatment A	14108.4203030	FALSE
## 30	9000	Treatment B	1662.5749298	TRUE
## 31	10000	Standard of Care	21683.5520638	FALSE
## 32	10000	Treatment A	16955.4851098	FALSE
## 33	10000	Treatment B	1518.4014762	TRUE
## 34	11000	Standard of Care	26082.7308806	FALSE
## 35	11000	Treatment A	19859.9980149	FALSE
## 36	11000	Treatment B	1431.6761210	TRUE
## 37	12000	Standard of Care	30514.9268393	FALSE
## 38	12000	Treatment A	22797.5280618	FALSE
## 39	12000	Treatment B	1377.9679075	TRUE
## 40	13000	Standard of Care	34964.0291731	FALSE
## 41	13000	Treatment A	25751.9644837	FALSE
## 42	13000	Treatment B	1341.1660692	TRUE
## 43	14000	Standard of Care	39426.3242783	FALSE
## 44	14000	Treatment A	28719.5936771	FALSE
## 45	14000	Treatment B	1317.5570022	TRUE
## 46	15000	Standard of Care	43901.4574252	FALSE
## 47	15000	Treatment A	31700.0609123	FALSE
## 48	15000	Treatment B	1306.7859770	TRUE
## 49	16000	Standard of Care	48389.2290587	FALSE
## 50	16000	Treatment A	34693.1666339	FALSE
## 51	16000	Treatment B	1308.6534383	TRUE
## 52	17000	Standard of Care	52880.6520160	FALSE
## 53	17000	Treatment A	37689.9236795	FALSE
## 54	17000	Treatment B	1314.1722236	TRUE
## 55	18000	Standard of Care	57375.4958769	FALSE
## 56	18000	Treatment A	40690.1016286	FALSE
## 57	18000	Treatment B	1323.1119123	TRUE
## 58	19000	Standard of Care	61874.4157034	FALSE
## 59	19000	Treatment A	43694.3555433	FALSE
## 60	19000	Treatment B	1336.1275667	TRUE
## 61	20000	Standard of Care	66377.8152919	FALSE
## 62	20000	Treatment A	46703.0892199	FALSE
## 63	20000	Treatment B	1353.6229831	TRUE

## 64	21000	Standard of Care	70883.4123263	FALSE
## 65	21000	Treatment A	49714.0203426	FALSE
## 66	21000	Treatment B	1373.3158454	TRUE
## 67	22000	Standard of Care	75390.4043422	FALSE
## 68	22000	Treatment A	52726.3464466	FALSE
## 69	22000	Treatment B	1394.4036891	TRUE
## 70	23000	Standard of Care	79898.9059040	FALSE
## 71	23000	Treatment A	55740.1820966	FALSE
## 72	23000	Treatment B	1417.0010788	TRUE
## 73	24000	Standard of Care	84408.1583602	FALSE
## 74	24000	Treatment A	58754.7686410	FALSE
## 75	24000	Treatment B	1440.3493629	TRUE
## 76	25000	Standard of Care	88918.3202306	FALSE
## 77	25000	Treatment A	61770.2645997	FALSE
## 78	25000	Treatment B	1464.6070612	TRUE
## 79	26000	Standard of Care	93429.7926390	FALSE
## 80	26000	Treatment A	64787.0710962	FALSE
## 81	26000	Treatment B	1490.1752974	TRUE
## 82	27000	Standard of Care	97941.9806019	FALSE
## 83	27000	Treatment A	67804.5931473	FALSE
## 84	27000	Treatment B	1516.4590882	TRUE
## 85	28000	Standard of Care	102454.6674043	FALSE
## 86	28000	Treatment A	70822.6140379	FALSE
## 87	28000	Treatment B	1543.2417185	TRUE
## 88	29000	Standard of Care	106968.1410388	FALSE
## 89	29000	Treatment A	73841.4217606	FALSE
## 90	29000	Treatment B	1570.8111808	TRUE
## 91	30000	Standard of Care	111481.6961882	FALSE
## 92	30000	Treatment A	76860.3109983	FALSE
## 93	30000	Treatment B	1598.4621581	TRUE

```
# ELC plot
gg_elc <- plot_exp_loss(elc_obj, log_y = FALSE,
  txtsize = txtsize, xlim = c(0, NA), n_x_ticks = 14,
  col = "full") +
  ggthemes::scale_color_colorblind() +
  ggthemes::scale_fill_colorblind() +
  # geom_point(aes(shape = as.name("Strategy")))) +
  scale_y_continuous("Expected Loss (Thousand $)",
    breaks = number_ticks(10),
    labels = function(x) x/1000) +
  theme(legend.position = c(0.4, 0.7),)
gg_elc
```



11.3.6 Expected value of perfect information (EVPI)

```
### Expected value of perfect information (EVPI)
evpi <- calc_evpi(wtp = v_wtp, psa = l_psa)
# EVPI plot
gg_evpi <- plot_evpi(evpi, effect_units = "QALY",
  txtsize = txtsize, xlim = c(0, NA), n_x_ticks = 14) +
  scale_y_continuous("EVPI (Thousand $)",
    breaks = number_ticks(10),
    labels = function(x) x/1000)
gg_evpi
```

