Markov Sick-Sicker model in R

With simulation-time dependency

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This Code adaptation Developed by the Decision Analysis in R for Technologies in Health (DARTH) workgroup.

This code implements a simulation-time-dependent Sick-Sicker cSTM model to conduct a CEA of two strategies: - Standard of Care (SoC): best available care for the patients with the disease. This scenario reflects the natural history of the disease
progression. - Strategy AB: This strategy combines treatment A and treatment B. The disease progression is reduced, and individuals in the Sick state have an
improved quality of life.

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

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

01 Load packages

```r
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", "ggrepel", "gridExtra"
# 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

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

03 Model input

```r
## General setup
cycle_length <- 1   # cycle length equal to one year (use 1/12 for monthly)
n_age_init   <- 25  # age at baseline
n_age_max    <- 100 # maximum age of follow up
n_cycles     <- (n_age_max - n_age_init)/cycle_length # time horizon, number of cycles
# Age labels
v_age_names  <- paste(rep(n_age_init:(n_age_max-1), each = 1/cycle_length),
                      1:(1/cycle_length),
                      sep = ".")
# the 4 health states of the model:
v_names_states <- c("H",  # Healthy (H)
                    "S1", # Sick (S1)
                    "S2", # Sicker (S2)
                    "D")  # Dead (D)

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
                 "Strategy AB")
n_str       <- length(v_names_str)   # number of strategies

## Within-cycle correction (WCC) using half-cycle rule
v_wcc  <- gen_wcc(n_cycles = n_cycles, method = "half-cycle")

### Transition rates (annual), and hazard ratios (HRs)
r_HS1  <- 0.15  # constant annual rate of becoming Sick when Healthy
r_S1H  <- 0.5   # constant annual rate of becoming Healthy when Sick
```

```
r_S1S2 <- 0.105 # constant annual rate 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

### Effectiveness of treatment AB
hr_S1S2_trtAB <- 0.6  # hazard ratio of becoming Sicker when Sick under treatment AB

## Age-dependent mortality rates
lt_usa_2015 <- read.csv("HMD_USA_Mx_2015.csv")
# Extract age-specific all-cause mortality for ages in model time horizon
v_r_mort_by_age <- lt_usa_2015 %>%
  dplyr::filter(Age >= n_age_init & Age < n_age_max) %>%
  dplyr::select(Total) %>%
  as.matrix()

### State rewards
#### Costs
c_H     <- 2000  # annual cost of being Healthy
c_S1    <- 4000  # annual cost of being Sick
c_S2    <- 15000 # annual cost of being Sicker
c_D     <- 0     # annual cost of being dead
c_trtAB <- 25000 # annual cost of receiving treatment AB
#### Utilities
u_H     <- 1     # annual utility of being Healthy
u_S1    <- 0.75  # annual utility of being Sick
u_S2    <- 0.5   # annual utility of being Sicker
u_D     <- 0     # annual utility of being dead
u_trtAB <- 0.95  # annual utility when receiving treatment AB

### Transition rewards
du_HS1  <- 0  # disutility when transitioning from Healthy to Sick
ic_HS1  <- 0  # increase in cost when transitioning from Healthy to Sick
ic_D    <- 0  # increase in cost when dying

### 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))

# Process model inputs
## Age-specific transition rates to the Dead state for all cycles
v_r_HDage  <- rep(v_r_mort_by_age, each = 1/cycle_length)
# Name age-specific mortality vector
names(v_r_HDage) <- v_age_names

# compute mortality rates
v_r_S1Dage  <- v_r_HDage * hr_S1 # Age-specific mortality rate in the Sick state
v_r_S2Dage  <- v_r_HDage * hr_S2 # Age-specific mortality rate in the Sicker state
v_r_S2Dage
```

```
##    25.1    26.1    27.1    28.1    29.1    30.1    31.1    32.1    33.1    34.1
## 0.01014 0.00999 0.01070 0.01087 0.01162 0.01167 0.01213 0.01289 0.01331 0.01375
##    35.1    36.1    37.1    38.1    39.1    40.1    41.1    42.1    43.1    44.1
## 0.01420 0.01490 0.01550 0.01616 0.01657 0.01747 0.01902 0.02052 0.02173 0.02395
##    45.1    46.1    47.1    48.1    49.1    50.1    51.1    52.1    53.1    54.1
## 0.02559 0.02807 0.03023 0.03349 0.03712 0.04085 0.04490 0.04905 0.05364 0.05806
##    55.1    56.1    57.1    58.1    59.1    60.1    61.1    62.1    63.1    64.1
## 0.06253 0.06775 0.07395 0.07895 0.08418 0.08974 0.09666 0.10456 0.11384 0.11838
##    65.1    66.1    67.1    68.1    69.1    70.1    71.1    72.1    73.1    74.1
## 0.12667 0.13593 0.14700 0.15732 0.17340 0.18758 0.20967 0.22917 0.24913 0.26767
##    75.1    76.1    77.1    78.1    79.1    80.1    81.1    82.1    83.1    84.1
## 0.29707 0.32412 0.35982 0.39238 0.43595 0.48727 0.53735 0.59911 0.66618 0.74051
##    85.1    86.1    87.1    88.1    89.1    90.1    91.1    92.1    93.1    94.1
## 0.82190 0.90754 1.03968 1.15093 1.24341 1.37872 1.54177 1.72393 1.94100 2.12654
##    95.1    96.1    97.1    98.1    99.1
## 2.43752 2.59087 2.87781 3.16429 3.39149
```

```
# transform rates to probabilities adjusting by cycle length
p_HS1       <- rate_to_prob(r = r_HS1,  t = cycle_length) # constant annual probability of becoming Sic
p_S1H       <- rate_to_prob(r = r_S1H,  t = cycle_length) # constant annual probability of becoming Hea
p_S1S2      <- rate_to_prob(r = r_S1S2, t = cycle_length) # constant annual probability of becoming Sic
v_p_HDage   <- rate_to_prob(v_r_HDage,  t = cycle_length) # Age-specific mortality risk in the Healthy 
v_p_S1Dage  <- rate_to_prob(v_r_S1Dage, t = cycle_length) # Age-specific mortality risk in the Sick sta
v_p_S2Dage  <- rate_to_prob(v_r_S2Dage, t = cycle_length) # Age-specific mortality risk in the Sicker s
v_p_S2Dage
```

```
##        25.1        26.1        27.1        28.1        29.1        30.1
## 0.010088764 0.009940266 0.010642959 0.010811135 0.011552749 0.011602170
##        31.1        32.1        33.1        34.1        35.1        36.1
## 0.012056728 0.012807280 0.013221814 0.013655901 0.014099656 0.014789544
##        37.1        38.1        39.1        40.1        41.1        42.1
## 0.015380493 0.016030128 0.016433473 0.017318284 0.018840261 0.020310898
##        43.1        44.1        45.1        46.1        47.1        48.1
## 0.021495604 0.023665475 0.025265351 0.027679698 0.029777643 0.032935418
##        49.1        50.1        51.1        52.1        53.1        54.1
## 0.036439499 0.040026885 0.043906914 0.047866478 0.052226757 0.056406670
##        55.1        56.1        57.1        58.1        59.1        60.1
## 0.060615119 0.065505932 0.071281871 0.075913872 0.080734227 0.085831162
##        61.1        62.1        63.1        64.1        65.1        66.1
## 0.092135372 0.099279247 0.107599271 0.111641588 0.118975637 0.127096266
##        67.1        68.1        69.1        70.1        71.1        72.1
## 0.136706023 0.145569403 0.159198773 0.171037201 0.189148217 0.204806661
##        73.1        74.1        75.1        76.1        77.1        78.1
## 0.220521365 0.234839758 0.257007999 0.276836542 0.302198081 0.324552605
##        79.1        80.1        81.1        82.1        83.1        84.1
## 0.353349942 0.385698851 0.415705417 0.450699704 0.486332957 0.523129351
##        85.1        86.1        87.1        88.1        89.1        90.1
## 0.560404371 0.596484347 0.646432194 0.683657566 0.711600902 0.748099220
##        91.1        92.1        93.1        94.1        95.1        96.1
## 0.785998018 0.821636201 0.856439682 0.880750817 0.912622721 0.925045199
##        97.1        98.1        99.1
## 0.943742167 0.957755876 0.966341512
```

```
## Annual transition probability of becoming Sicker when Sick for treatment AB
# Apply hazard ratio to rate to obtain transition rate of becoming Sicker when Sick for treatment AB
r_S1S2_trtAB <- r_S1S2 * hr_S1S2_trtAB
# Transform rate to probability to become Sicker when Sick under treatment AB
# adjusting by cycle length conditional on surviving
p_S1S2_trtAB <- rate_to_prob(r = r_S1S2_trtAB, t = cycle_length)
```

04 Construct state-transition models

04.1 Initial state vector

```r
# All starting healthy
v_m_init <- c(H = 1, S1 = 0, S2 = 0, D = 0) # initial state vector
v_m_init
```

```
##  H S1 S2  D
##  1  0  0  0
```

04.2 Initialize cohort traces

```r
### Initialize cohort trace under SoC
m_M_SoC <- matrix(NA,
              nrow = (n_cycles + 1), ncol = n_states,
              dimnames = list(0:n_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 trace for strategy AB
# Structure and initial states are the same as for SoC
m_M_strAB <- m_M_SoC # Strategy AB
```

04.3 Create transition probability matrices

```r
## Create transition probability arrays for strategy SoC
### Initialize transition probability array for strategy SoC
# All transitions to a non-death state are assumed to be conditional on survival
a_P_SoC <- array(0,
                 dim  = c(n_states, n_states, n_cycles),
                 dimnames = list(v_names_states,
                                 v_names_states,
                                 0:(n_cycles - 1)))
### Fill in array
## From H
a_P_SoC["H", "H", ]   <- (1 - v_p_HDage) * (1 - p_HS1)
a_P_SoC["H", "S1", ]  <- (1 - v_p_HDage) *      p_HS1
a_P_SoC["H", "D", ]   <-      v_p_HDage
## From S1
a_P_SoC["S1", "H", ]  <- (1 - v_p_S1Dage) *       p_S1H
a_P_SoC["S1", "S1", ] <- (1 - v_p_S1Dage) * (1 - (p_S1H + p_S1S2))
a_P_SoC["S1", "S2", ] <- (1 - v_p_S1Dage) *               p_S1S2
a_P_SoC["S1", "D", ]  <-      v_p_S1Dage
## From S2
a_P_SoC["S2", "S2", ] <- 1 - v_p_S2Dage
a_P_SoC["S2", "D", ]  <-     v_p_S2Dage
## From D
a_P_SoC["D", "D", ]   <- 1

### Initialize transition probability array for strategy AB
a_P_strAB <- a_P_SoC
# Update only transition probabilities from S1 involving p_S1S2
```

```r
a_P_strAB["S1", "S1", ] <- (1 - v_p_S1Dage) * (1 - (p_S1H + p_S1S2_trtAB))
a_P_strAB["S1", "S2", ] <- (1 - v_p_S1Dage) *               p_S1S2_trtAB

## Check if transition probability arrays are valid
### Check that transition probabilities are [0, 1]
check_transition_probability(a_P_SoC,   verbose = TRUE)
check_transition_probability(a_P_strAB, verbose = TRUE)
### Check that all rows for each slice of the array sum to 1
check_sum_of_transition_array(a_P_SoC,   n_states = n_states, n_cycles = n_cycles, verbose = TRUE)
check_sum_of_transition_array(a_P_strAB, n_states = n_states, n_cycles = n_cycles, verbose = TRUE)
```

04.4 Create transition dynamics arrays

```r
# These arrays will capture transitions from each state to another over time
### Initialize transition dynamics array for strategy SoC
a_A_SoC <- array(0,
             dim      = c(n_states, n_states, n_cycles + 1),
             dimnames = list(v_names_states, v_names_states, 0:n_cycles))
# Set first slice of a_A_SoC with the initial state vector in its diagonal
diag(a_A_SoC[, , 1]) <- v_m_init
### Initialize transition-dynamics array for strategy AB
# Structure and initial states are the same as for SoC
a_A_strAB <- a_A_SoC
```

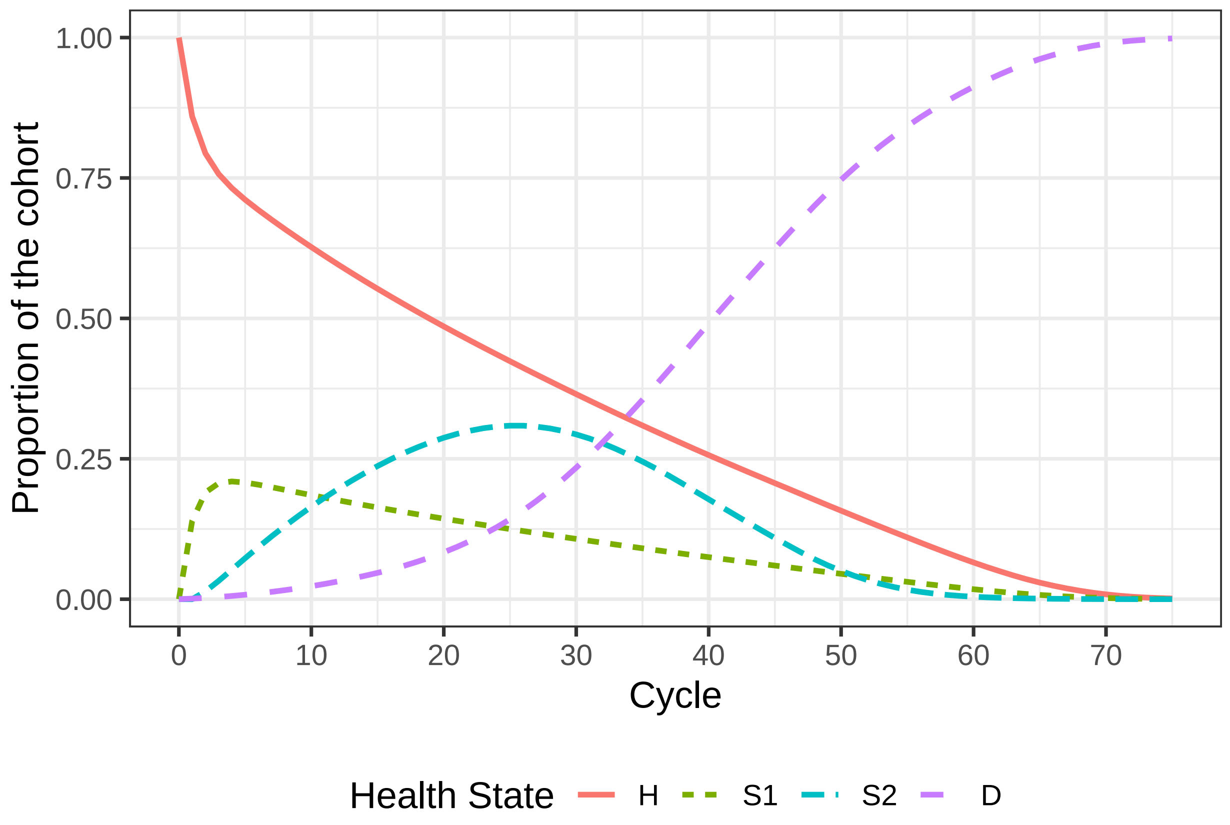
05 Run Markov model

```r
# Iterative solution of age-dependent cSTM
for(t in 1:n_cycles){
  ## Fill in cohort trace
  # For SoC
  m_M_SoC[t + 1, ]   <- m_M_SoC[t, ]   %*% a_P_SoC[, , t]
  # For strategy AB
  m_M_strAB[t + 1, ] <- m_M_strAB[t, ] %*% a_P_strAB[, , t]

  ## Fill in transition-dynamics array
  # For SoC
  a_A_SoC[, , t + 1]   <- diag(m_M_SoC[t, ])   %*% a_P_SoC[, , t]
  # For strategy AB
  a_A_strAB[, , t + 1] <- diag(m_M_strAB[t, ]) %*% a_P_strAB[, , t]
}

## Store the cohort traces in a list
l_m_M <- list(SoC =  m_M_SoC,
              AB  =  m_M_strAB)
names(l_m_M) <- v_names_str

## Store the transition dynamics array for each strategy in a list
l_a_A <- list(SoC =  a_A_SoC,
              AB  =  a_A_strAB)
names(l_a_A) <- v_names_str
```

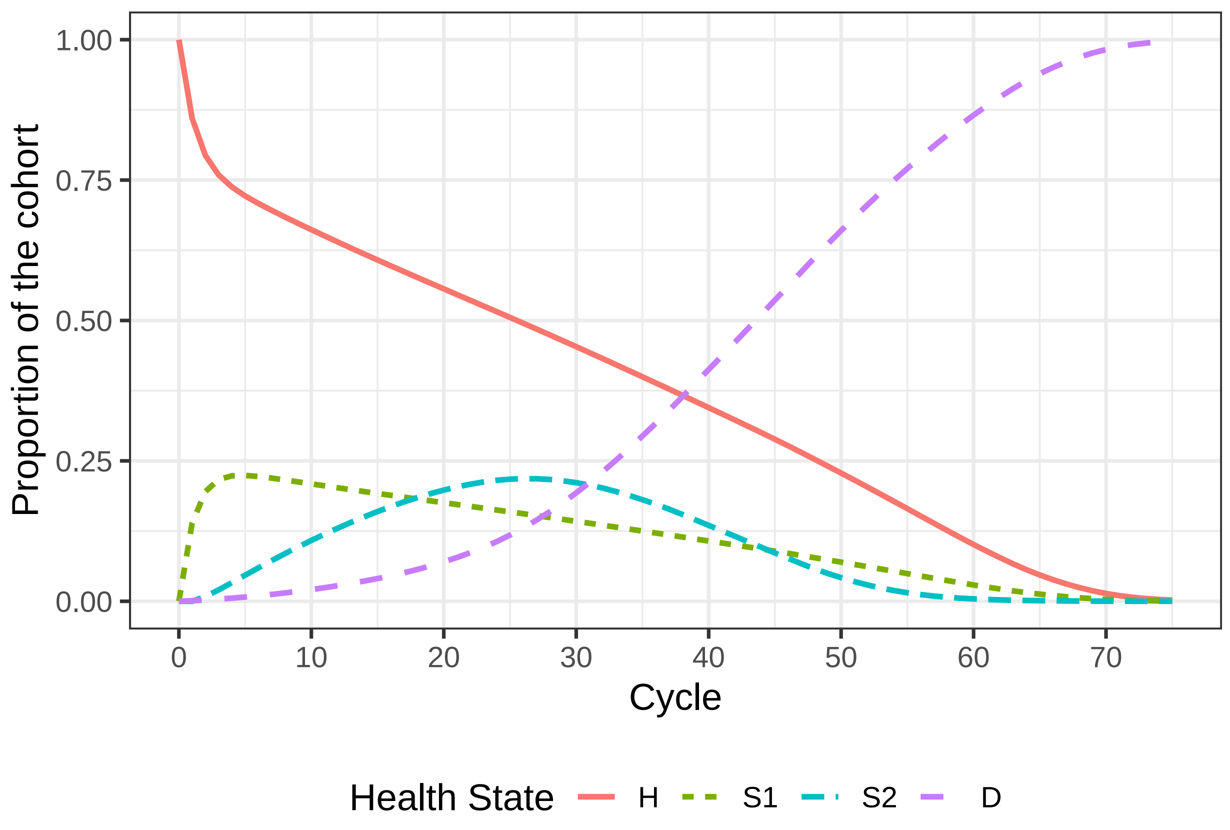
06 Plot Outputs

06.1 Plot the cohort trace for strategies SoC and AB

```
plot_trace(m_M_SoC)
```



```
plot_trace(m_M_strAB)
```



07 State Rewards

```
## Scale by the cycle length
# Vector of state utilities under strategy SoC
v_u_SoC    <- c(H  = u_H,
                S1 = u_S1,
                S2 = u_S2,
                D  = u_D) * cycle_length
# Vector of state costs under strategy SoC
v_c_SoC    <- c(H  = c_H,
                S1 = c_S1,
                S2 = c_S2,
                D  = c_D) * cycle_length
# Vector of state utilities under strategy AB
v_u_strAB  <- c(H  = u_H,
                S1 = u_trtAB,
                S2 = u_S2,
                D  = u_D) * cycle_length
# Vector of state costs under strategy AB
v_c_strAB  <- c(H  = c_H,
                S1 = c_S1 + c_trtAB,
                S2 = c_S2 + c_trtAB,
                D  = c_D) * cycle_length

## Store state rewards
```

```r
# Store the vectors of state utilities for each strategy in a list
l_u <- list(SoC = v_u_SoC,
            AB  = v_u_strAB)
# Store the vectors of state cost for each strategy in a list
l_c <- list(SoC =  v_c_SoC,
            AB  =  v_c_strAB)

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

08 Compute expected outcomes

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

## Loop through each strategy and calculate total utilities and costs
for (i in 1:n_str) { # i <- 1
  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
  a_A_str <- l_a_A[[i]] # select the transition array for the i-th strategy

  ## Array of state rewards
  # Create transition matrices of state utilities and state costs for the i-th strategy
  m_u_str   <- matrix(v_u_str, nrow = n_states, ncol = n_states, byrow = T)
  m_c_str   <- matrix(v_c_str, nrow = n_states, ncol = n_states, byrow = T)
  # Expand the transition matrix of state utilities across cycles to form a transition array of state u
  a_R_u_str <- array(m_u_str,
                     dim      = c(n_states, n_states, n_cycles + 1),
                     dimnames = list(v_names_states, v_names_states, 0:n_cycles))
  # Expand the transition matrix of state costs across cycles to form a transition array of state costs
  a_R_c_str <- array(m_c_str,
                     dim      = c(n_states, n_states, n_cycles + 1),
                     dimnames = list(v_names_states, v_names_states, 0:n_cycles))

  ## Apply transition rewards
  # Apply disutility due to transition from H to S1
  a_R_u_str["H", "S1", ]      <- a_R_u_str["H", "S1", ]       - du_HS1
  # Add transition cost per cycle due to transition from H to S1
  a_R_c_str["H", "S1", ]      <- a_R_c_str["H", "S1", ]       + ic_HS1
  # Add transition cost  per cycle of dying from all non-dead states
  a_R_c_str[-n_states, "D", ] <- a_R_c_str[-n_states, "D", ] + ic_D

  ### Expected QALYs and costs for all transitions per cycle
  # QALYs = life years x QoL
  # Note: all parameters are annual in our example. In case your own case example is different make sur
  a_Y_c_str <- a_A_str * a_R_c_str
  a_Y_u_str <- a_A_str * a_R_u_str

  ### Expected QALYs and costs per cycle
  ## Vector of QALYs and costs
  v_qaly_str <- apply(a_Y_u_str, 3, sum) # sum the proportion of the cohort across transitions
  v_cost_str <- apply(a_Y_c_str, 3, sum) # sum the proportion of the cohort across transitions

  ## Discounted total expected QALYs and Costs per strategy and apply within-cycle correction if applic
  # 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)
}
```

09 Cost-effectiveness analysis (CEA)

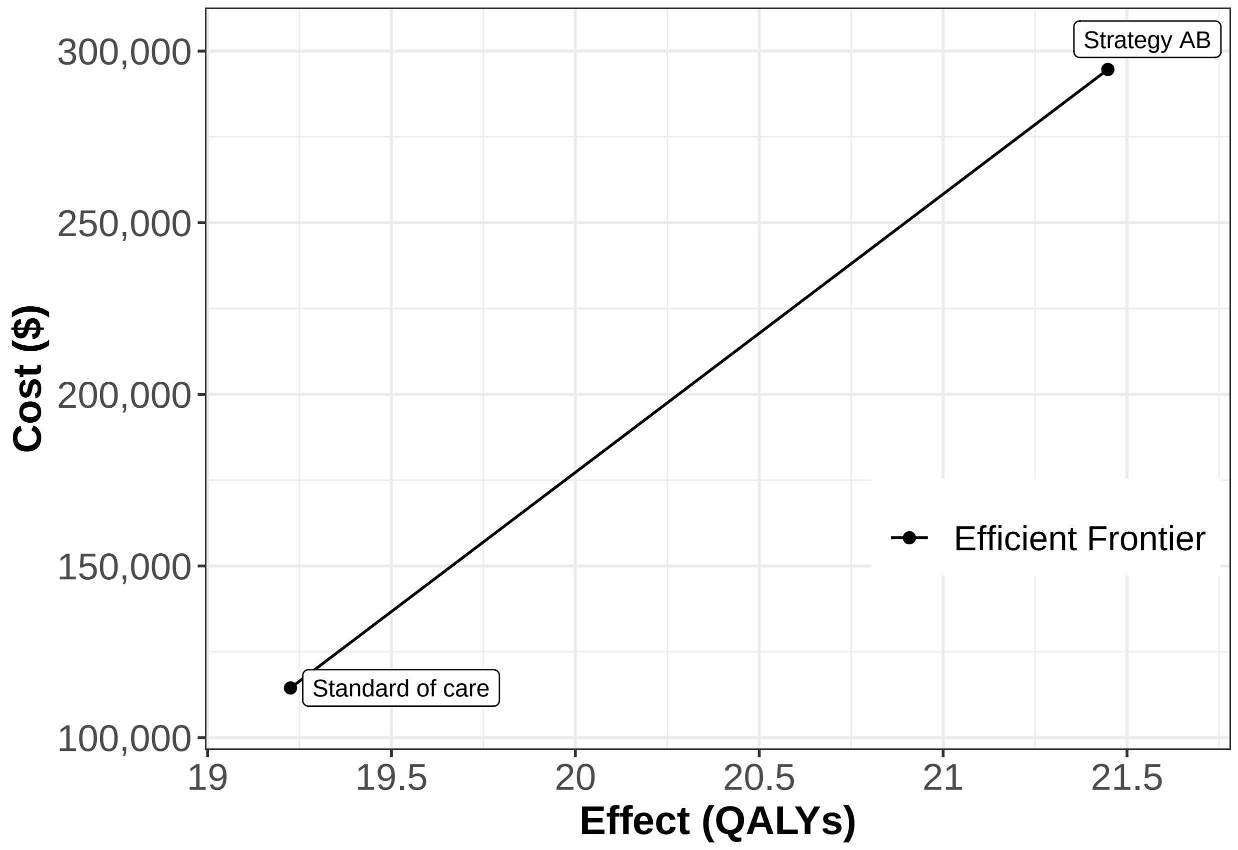
```
## Incremental cost-effectiveness ratios (ICERs)
df_cea <- calculate_icers(cost       = v_tot_cost,
                          effect     = v_tot_qaly,
                          strategies = v_names_str)
df_cea
```

```
##                          Strategy     Cost   Effect Inc_Cost Inc_Effect
## Standard of care Standard of care 114473.9 19.22543       NA         NA
## Strategy AB           Strategy AB 294643.4 21.44797 180169.6   2.222541
##                      ICER Status
## Standard of care       NA     ND
## Strategy AB      81064.67     ND
```

```
## 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   114,474 19.23                  <NA>
## Strategy AB           Strategy AB   294,643 21.45               180,170
##                  Incremental QALYs ICER ($/QALY) Status
## Standard of care                NA          <NA>     ND
## Strategy AB                   2.22        81,065     ND
```

```
## CEA frontier
plot(df_cea, label = "all", txtsize = 16) +
  expand_limits(x = max(table_cea$QALYs) + 0.1) +
  theme(legend.position = c(0.82, 0.3))
```



10 Deterministic Sensitivity Analysis (DSA)

```
## Load model, CEA and PSA functions
source('Functions_markov_sick-sicker_time.R')
```

10.1 Model input for SA

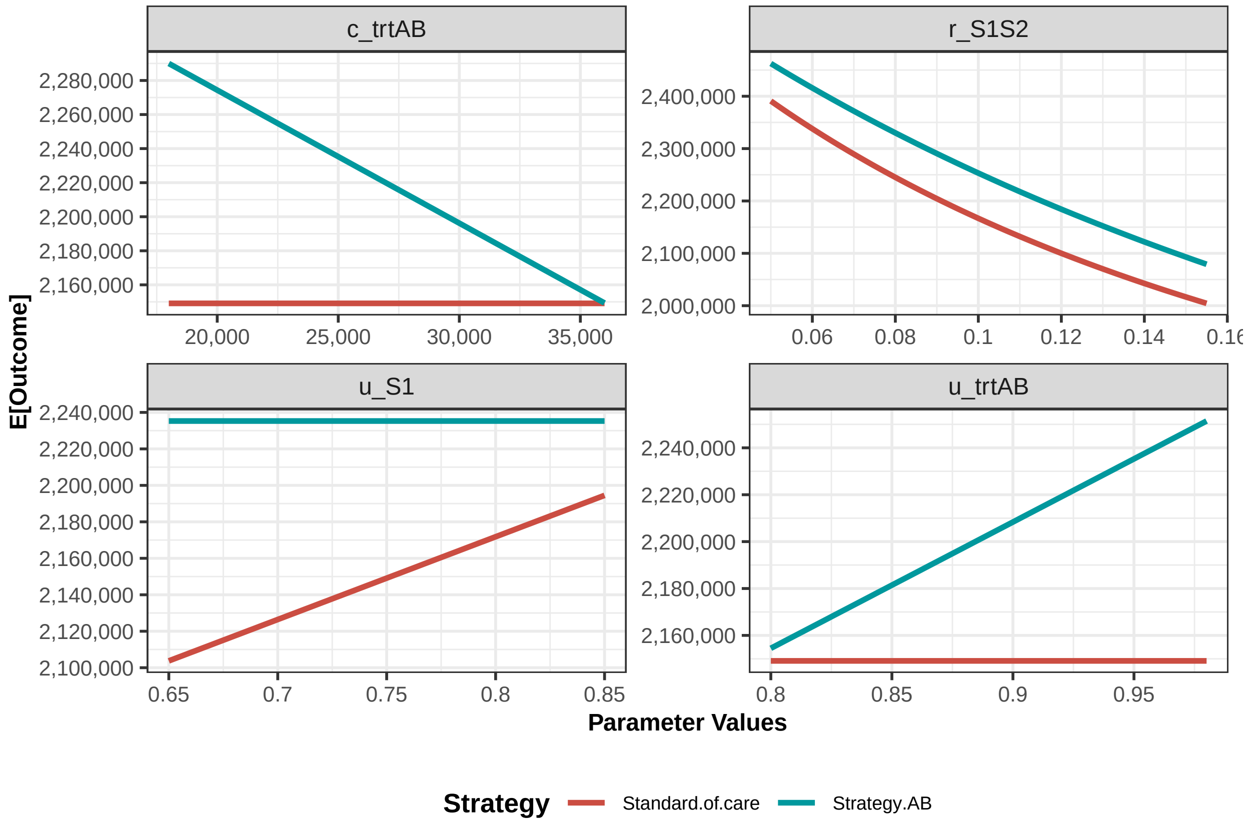
```
## List of input parameters
l_params_all <- list(
  # Transition probabilities (per cycle), hazard ratios
  v_r_HDage = v_r_HDage, # constant rate of dying when Healthy (all-cause mortality)
  r_HS1     = 0.15,      # constant annual rate of becoming Sick when Healthy conditional on surviving
  r_S1H     = 0.5,       # constant annual rate of becoming Healthy when Sick conditional on surviving
  r_S1S2    = 0.105,     # constant annual rate of becoming Sicker when Sick conditional on surviving
  hr_S1     = 3,         # hazard ratio of death in Sick vs Healthy
  hr_S2     = 10,        # hazard ratio of death in Sicker vs Healthy
  # Effectiveness of treatment AB
  hr_S1S2_trtAB = 0.6,   # hazard ratio of becoming Sicker when Sick under treatment AB
  ## State rewards
  # Costs
  c_H       = 2000,      # cost of remaining one cycle in Healthy
  c_S1      = 4000,      # cost of remaining one cycle in Sick
  c_S2      = 15000,     # cost of remaining one cycle in Sicker
  c_D       = 0,         # cost of being dead (per cycle)
  c_trtAB   = 25000,      # cost of treatment A
  # Utilities
  u_H       = 1,          # utility when Healthy
  u_S1      = 0.75,       # utility when Sick
  u_S2      = 0.5,        # utility when Sicker
  u_D       = 0,          # utility when Dead
  u_trtAB   = 0.95,       # utility when being treated with A
  ## Transition rewards
  du_HS1    = 0.01,       # disutility when transitioning from Healthy to Sick
  ic_HS1    = 1000,       # increase in cost when transitioning from Healthy to Sick
  ic_D      = 2000,       # increase in cost when dying
  # Initial and maximum ages
  n_age_init = 25,
  n_age_max  = 100,
  # Discount rates
  d_c        = 0.03,      # annual discount rate for costs
  d_e        = 0.03,      # annual discount rate for QALYs,
  # Cycle length
  cycle_length = 1
)
```

10.2 One-way sensitivity analysis (OWSA)

```
options(scipen = 999) # disabling scientific notation in R
# data.frame 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("r_S1S2", "c_trtAB", "u_S1", "u_trtAB"),
                             min  = c(0.05 , 18000 , 0.65, 0.80), # min parameter values
                             max  = c(0.155, 36000 , 0.85, 0.98)  # max parameter values
                             )

owsa_nmb  <- run_owsa_det(params_range    = df_params_owsa,    # data.frame 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           = 120000)            # extra argument to pass to FUN
```

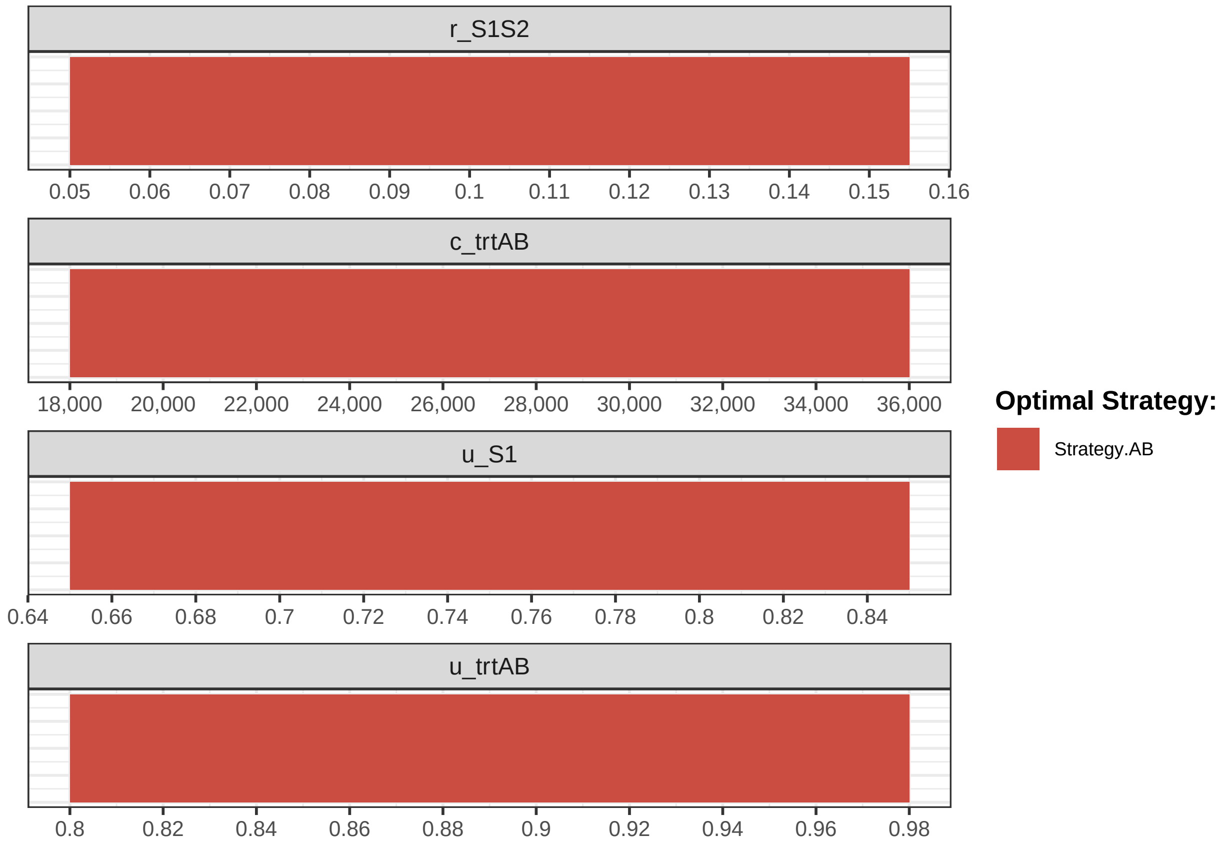
```
##   |                                                                              |
```

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



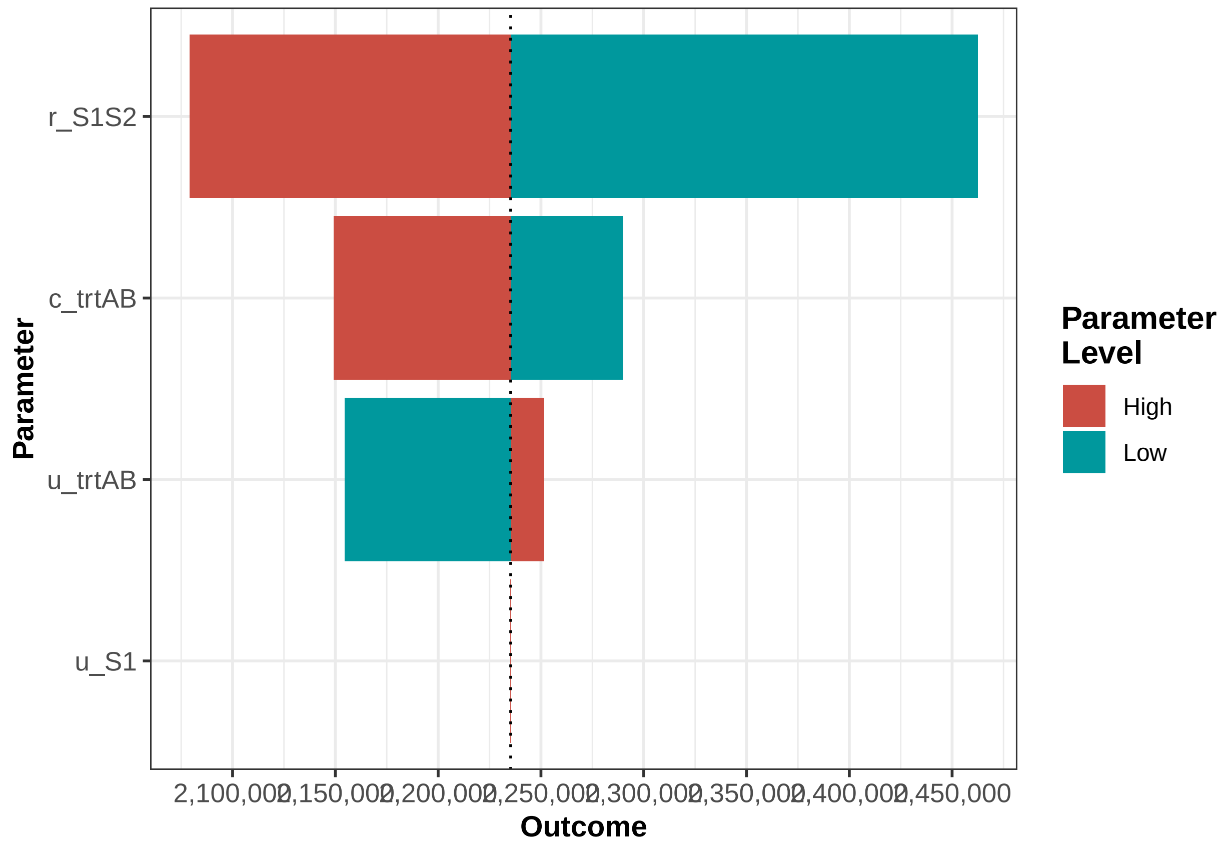
10.2.1 Optimal strategy with OWSA

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



10.2.2 Tornado plot

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

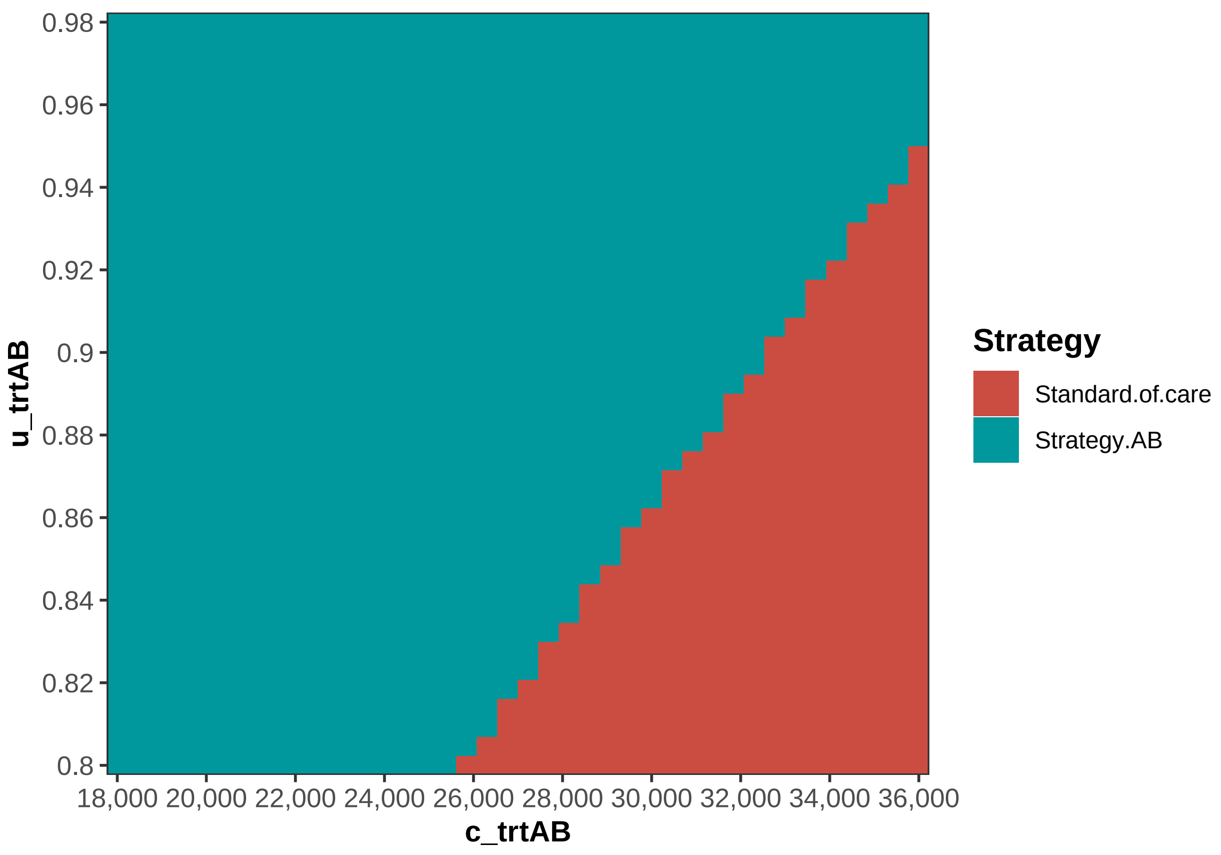


10.3 Two-way sensitivity analysis (TWSA)

```
# 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_trtAB", "u_trtAB"),
                             min  = c(18000, 0.80),  # min parameter values
                             max  = c(36000, 0.98)   # max parameter values
                             )

twsa_nmb <- run_twsa_det(params_range    = df_params_twsa,    # data.frame 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        = c("NMB"),          # output to do the TWSA on
                         strategies      = v_names_str,       # names of the strategies
                         n_wtp           = 120000)            # extra argument to pass to FUN
```

```
##   |                                                                              |
```

```
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)
```

```
##                          Strategy     Cost   Effect     NMB
## Standard of care Standard of care 116374.4 18.87920 1771545
## Strategy AB           Strategy AB 296300.3 21.09653 1813352
```

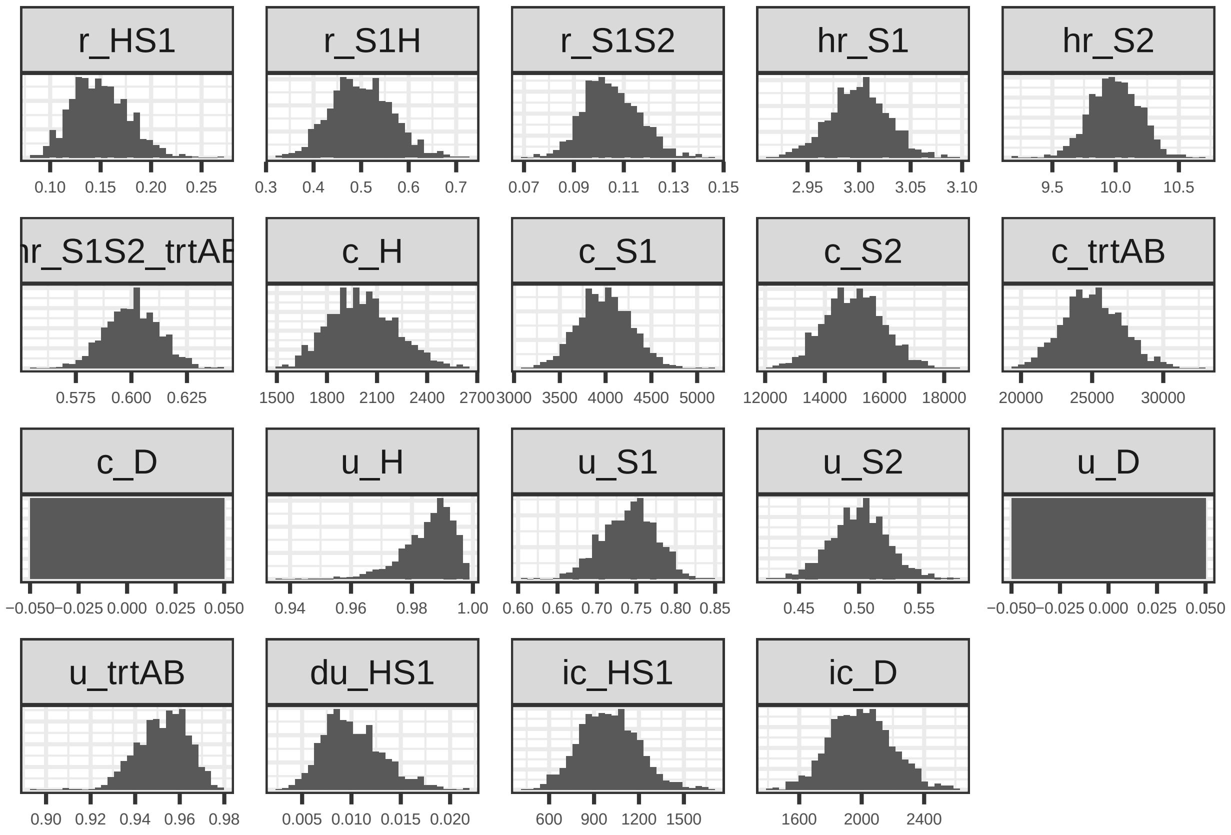
```
# Test function to generate PSA input dataset
generate_psa_params(10)
```

```
##        r_HS1     r_S1H      r_S1S2    hr_S1     hr_S2 hr_S1S2_trtAB      c_H
## 1  0.1879013 0.4801301 0.10796555 3.000891 10.137621     0.5787234 1969.304
## 2  0.1487534 0.4461028 0.11015130 2.977455  9.720297     0.5895503 1641.192
## 3  0.1240989 0.4277723 0.12019699 3.019838 10.140862     0.5994554 2276.032
## 4  0.1207401 0.6823019 0.10356461 2.986256 10.506942     0.5933100 1717.867
## 5  0.1407570 0.4834377 0.10607418 2.964711 10.186604     0.6094500 2132.549
## 6  0.1444703 0.5199434 0.09743299 2.979785 10.290916     0.5985713 2113.222
## 7  0.1298975 0.4864323 0.11804713 2.984690 10.307978     0.5986025 2123.062
## 8  0.1953886 0.5546269 0.09521281 3.041686  9.847810     0.5952682 2387.026
## 9  0.1092301 0.5654439 0.11498572 2.983202 10.073315     0.5858269 1600.231
## 10 0.1824868 0.4388704 0.09804320 3.044841 10.093864     0.6101527 1916.467
##        c_S1     c_S2   c_trtAB c_D       u_H      u_S1      u_S2 u_D    u_trtAB
## 1  3970.522 15303.55 27747.45   0 0.9832065 0.7169406 0.4628316   0 0.9456881
## 2  3680.588 15378.20 25209.56   0 0.9917677 0.7851270 0.4504530   0 0.9093339
## 3  3781.956 15614.73 25142.62   0 0.9727485 0.7582961 0.4727426   0 0.9390084
## 4  3448.146 15401.50 24697.69   0 0.9836544 0.7648816 0.4851046   0 0.9537789
## 5  4656.666 15198.97 22459.38   0 0.9915345 0.7751203 0.5311969   0 0.9577708
## 6  3879.536 14070.22 27794.29   0 0.9964569 0.7757487 0.5155318   0 0.9582262
## 7  3911.558 16006.75 25340.20   0 0.9795568 0.7965897 0.5041742   0 0.9349559
## 8  4497.693 15402.85 26952.90   0 0.9896162 0.7381845 0.4668479   0 0.9412370
## 9  4198.111 16322.33 23576.54   0 0.9743259 0.7235973 0.4723743   0 0.9570896
## 10 4087.810 15848.52 24120.75   0 0.9827154 0.7573872 0.5319503   0 0.9618487
##         du_HS1    ic_HS1     ic_D
## 1  0.008412808  792.4331 1939.526
## 2  0.010606291  926.6452 2048.008
## 3  0.010531334  838.5385 2807.393
## 4  0.009906859 1048.1656 1764.510
## 5  0.011257731  875.4987 2162.258
## 6  0.016727498 1092.0825 1808.114
## 7  0.010509535 1037.3152 2368.812
## 8  0.009053723  809.3469 2073.669
## 9  0.012068970 1130.1533 1974.209
## 10 0.011478733 1108.5800 2059.040
```

```
## 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)
```

```
##       r_HS1     r_S1H      r_S1S2    hr_S1     hr_S2 hr_S1S2_trtAB      c_H
## 1 0.1879013 0.5386300 0.11118482 2.984211  9.955194     0.5967508 1976.371
## 2 0.1487534 0.5341772 0.08823294 3.032752  9.655530     0.6382210 1919.375
## 3 0.1240989 0.5081914 0.10561891 3.005960 10.210922     0.6055352 2119.283
## 4 0.1207401 0.5807883 0.10238229 3.021883  9.896945     0.6157481 2591.358
## 5 0.1407570 0.5669941 0.09952737 2.939640  9.863104     0.6024367 2250.708
## 6 0.1444703 0.5624339 0.12142602 2.982949 10.108564     0.5975063 2504.241
##       c_S1     c_S2   c_trtAB c_D       u_H      u_S1      u_S2 u_D    u_trtAB
## 1 3932.928 15714.69 25348.12   0 0.9950597 0.6992784 0.5018781   0 0.9728172
## 2 3843.274 14724.57 24976.52   0 0.9795858 0.7503645 0.5000770   0 0.9531826
## 3 4314.533 18349.98 28545.94   0 0.9765326 0.6703114 0.4778468   0 0.9593837
## 4 3903.295 15191.92 23475.91   0 0.9849616 0.7582911 0.4750196   0 0.9379568
## 5 4132.504 15029.64 20168.13   0 0.9864103 0.7889100 0.4999208   0 0.9376958
## 6 3961.236 16738.03 25931.16   0 0.9734870 0.7256934 0.4970604   0 0.9607761
##        du_HS1    ic_HS1     ic_D
## 1 0.012672847  922.6349 1851.850
## 2 0.007971746 1075.9420 1970.602
## 3 0.006323387 1138.3535 2035.958
## 4 0.010696387 1108.6087 2071.939
## 5 0.010152628 1128.2519 1937.251
## 6 0.008681084  905.7657 1982.216
```

```
### 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))
```

```r
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 = " "))
  }
}
```

```
##  1 % done 2 % done 3 % done 4 % done 5 % done 6 % done 7 % done 8 % done 9 % done 10 % done 11 % don
```

```r
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)))
```

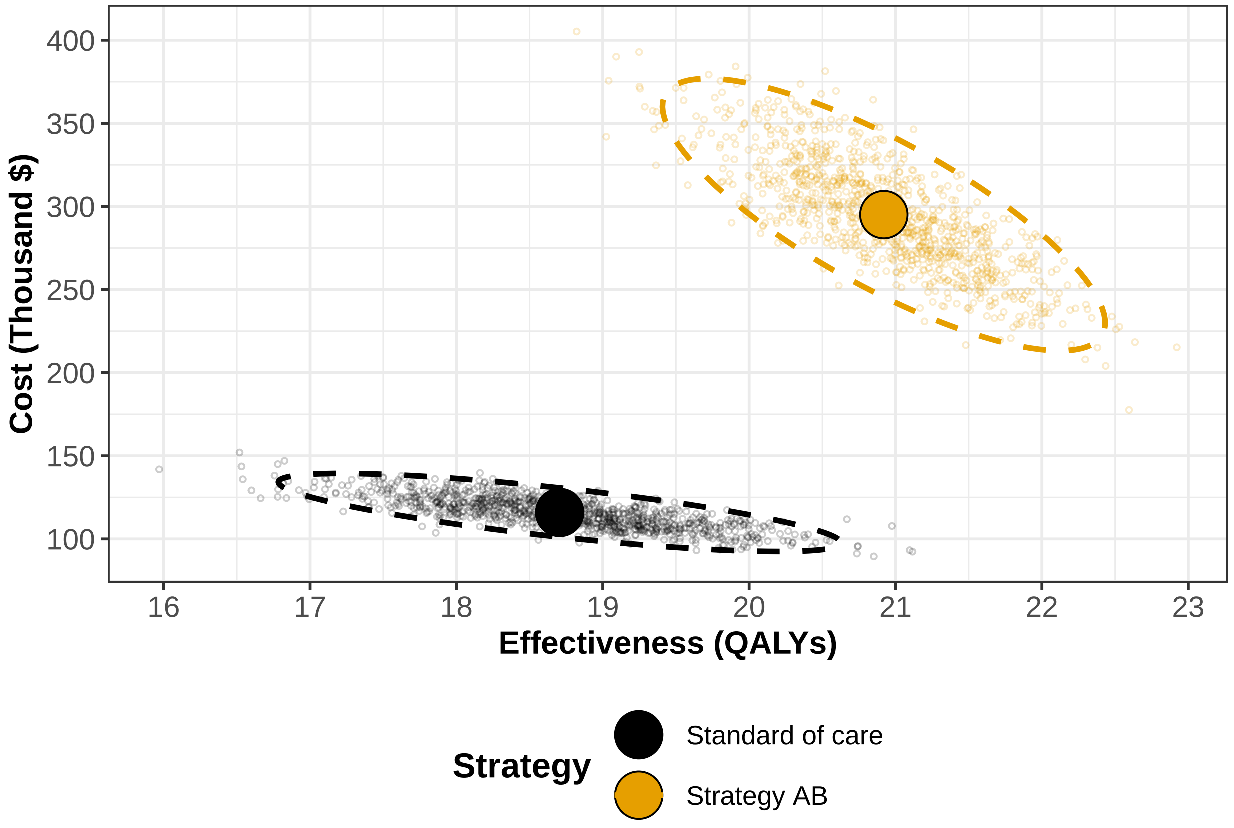
```
## [1] "PSA with 1,000 simulations run in series in 4.81 secs"
```

11.3 Visualize PSA results for CEA

```r
### 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, 200000, by = 5000)
```

11.3.1 Cost-Effectiveness Scatter plot

```r
### 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
```



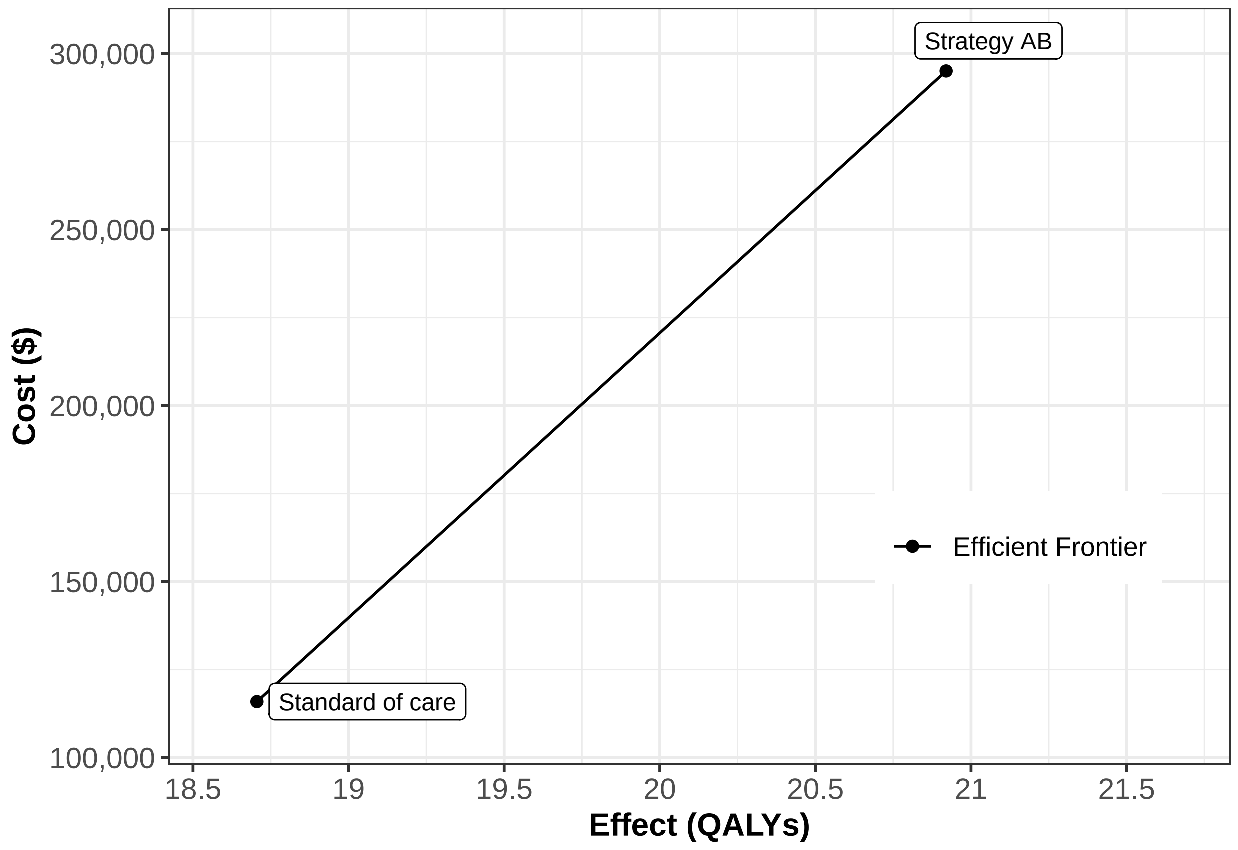
11.3.2 Incremental cost-effectiveness ratios (ICERs) with probabilistic output

```
### 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 115908.2 18.70547       NA         NA       NA     ND
## 2      Strategy AB 295075.0 20.92011 179166.8   2.214639 80901.14     ND
```

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))
```

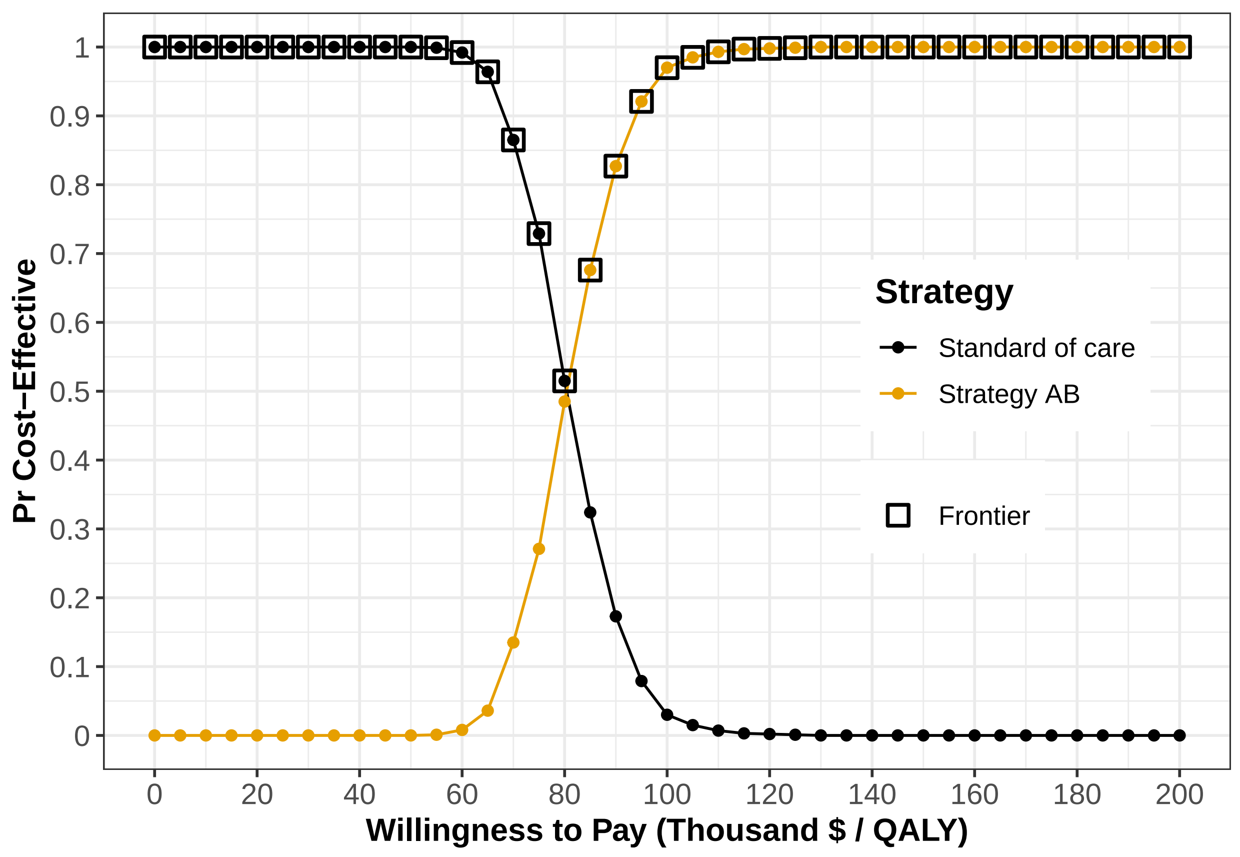


11.3.4 Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)

```
### 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     85000 Standard of care
## 2     85000    200000      Strategy AB
```

```
# 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
```

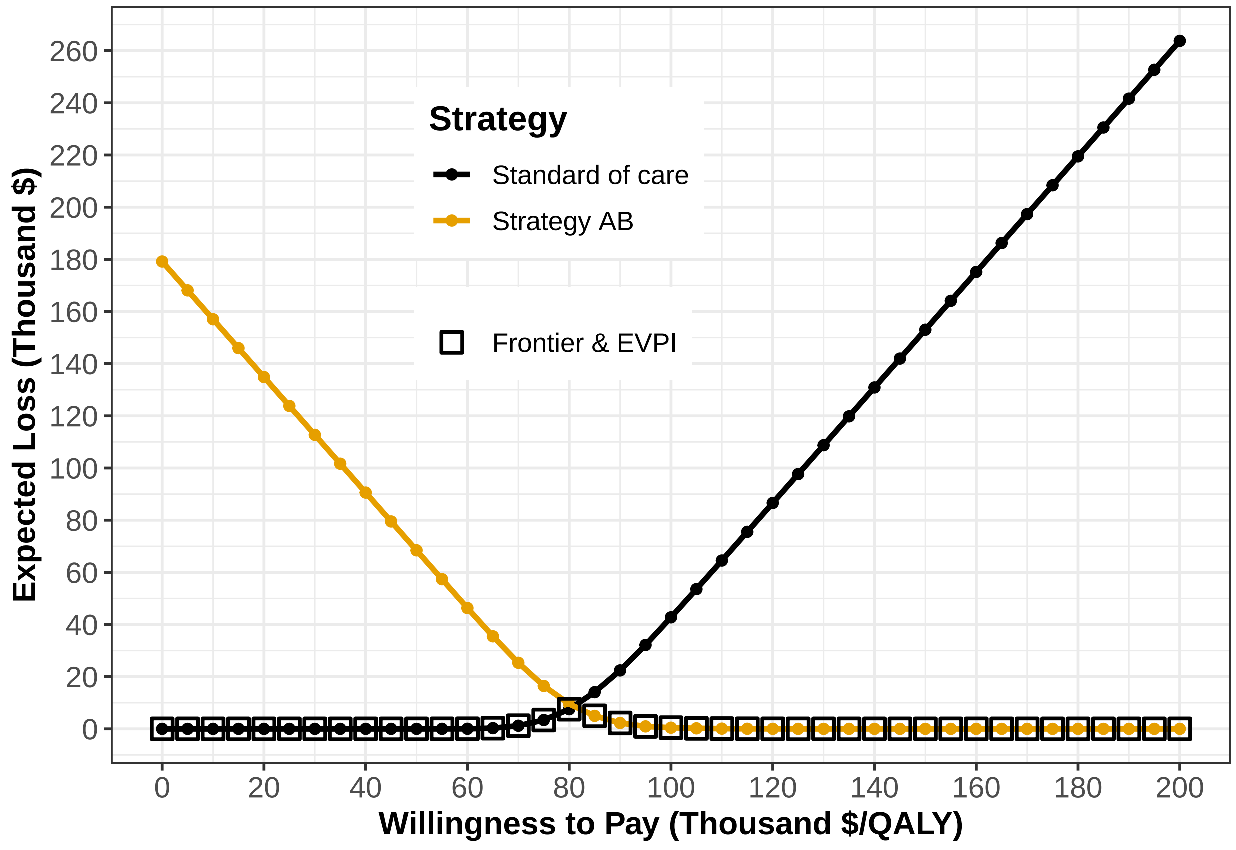


11.3.5 Expected Loss Curves (ELCs)

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

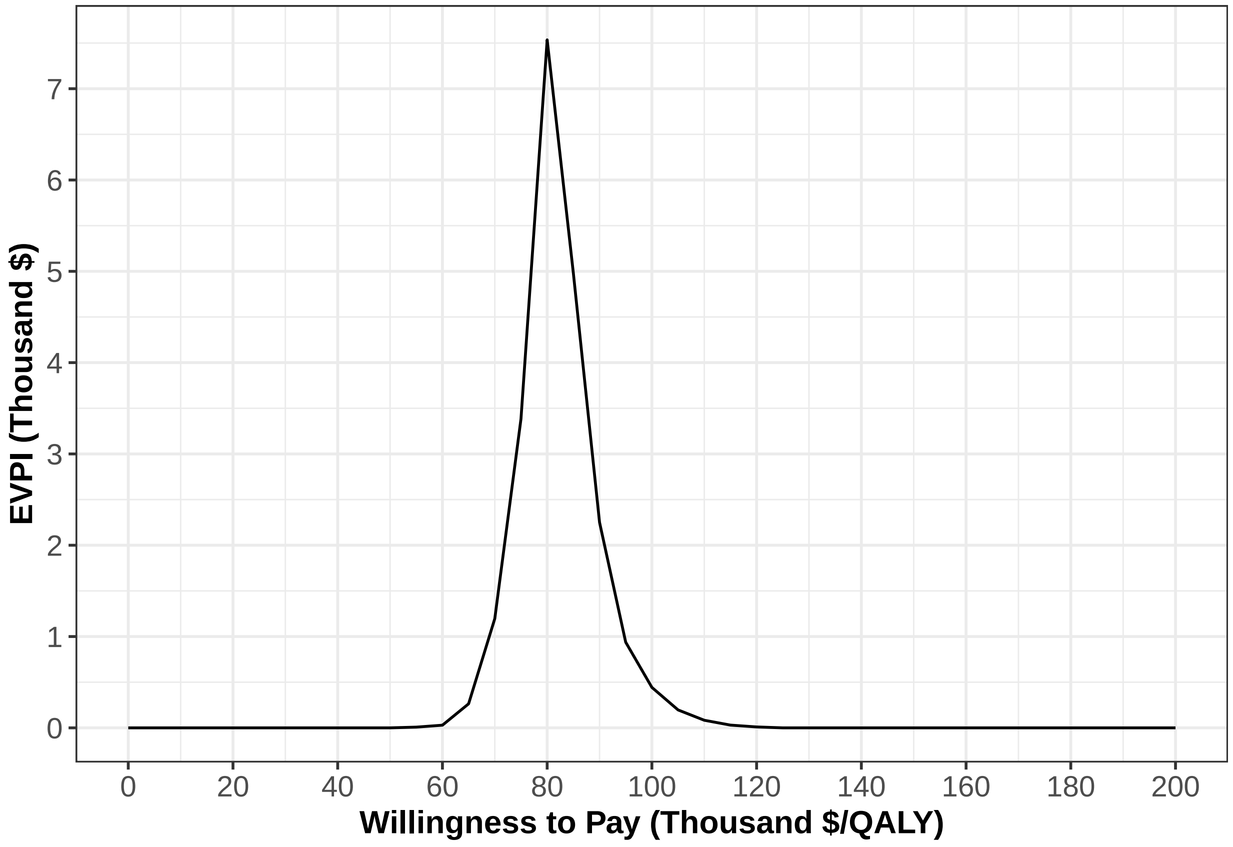
```
##        WTP         Strategy   Expected_Loss On_Frontier
## 1        0 Standard of care      0.00000000        TRUE
## 2        0      Strategy AB 179166.84111189       FALSE
## 3     5000 Standard of care      0.00000000        TRUE
## 4     5000      Strategy AB 168093.64420636       FALSE
## 5    10000 Standard of care      0.00000000        TRUE
## 6    10000      Strategy AB 157020.44730082       FALSE
## 7    15000 Standard of care      0.00000000        TRUE
## 8    15000      Strategy AB 145947.25039529       FALSE
## 9    20000 Standard of care      0.00000000        TRUE
## 10   20000      Strategy AB 134874.05348975       FALSE
## 11   25000 Standard of care      0.00000000        TRUE
## 12   25000      Strategy AB 123800.85658422       FALSE
## 13   30000 Standard of care      0.00000000        TRUE
## 14   30000      Strategy AB 112727.65967868       FALSE
## 15   35000 Standard of care      0.00000000        TRUE
## 16   35000      Strategy AB 101654.46277314       FALSE
## 17   40000 Standard of care      0.00000000        TRUE
## 18   40000      Strategy AB  90581.26586761       FALSE
## 19   45000 Standard of care      0.00000000        TRUE
## 20  45000       Strategy AB  79508.06896207       FALSE
## 21  50000 Standard of care      0.00000000        TRUE
## 22  50000       Strategy AB  68434.87205654       FALSE
## 23  55000 Standard of care      7.79331782        TRUE
## 24  55000       Strategy AB  57369.46846883       FALSE
## 25  60000 Standard of care     28.95908467        TRUE
## 26  60000       Strategy AB  46317.43733014       FALSE
## 27  65000 Standard of care    263.13980366        TRUE
## 28  65000       Strategy AB  35478.42114360       FALSE
## 29  70000 Standard of care   1195.75830262        TRUE
## 30  70000       Strategy AB  25337.84273702       FALSE
## 31  75000 Standard of care   3383.87077235        TRUE
## 32  75000       Strategy AB  16452.75830121       FALSE
## 33  80000 Standard of care   7534.96974238        TRUE
## 34  80000       Strategy AB   9530.66036570       FALSE
## 35  85000 Standard of care  14058.14964550       FALSE
## 36  85000       Strategy AB   4980.64336329        TRUE
## 37  90000 Standard of care  22401.51600768       FALSE
## 38  90000       Strategy AB   2250.81281993        TRUE
## 39  95000 Standard of care  32161.76748056       FALSE
## 40  95000       Strategy AB    937.86738728        TRUE
## 41 100000 Standard of care  42740.07083657       FALSE
## 42 100000       Strategy AB    442.97383775        TRUE
## 43 105000 Standard of care  53566.36291415       FALSE
## 44 105000       Strategy AB    196.06900980        TRUE
## 45 110000 Standard of care  64526.51511177       FALSE
## 46 110000       Strategy AB     83.02430188        TRUE
## 47 115000 Standard of care  75546.59381131       FALSE
## 48 115000       Strategy AB     29.90609589        TRUE
## 49 120000 Standard of care  86599.80991635       FALSE
## 50 120000       Strategy AB      9.92529539        TRUE
## 51 125000 Standard of care  97663.09274292       FALSE
## 52 125000       Strategy AB      0.01121643        TRUE
## 53 130000 Standard of care 108736.27843203       FALSE
## 54 130000       Strategy AB      0.00000000        TRUE
## 55 135000 Standard of care 119809.47533757       FALSE
## 56 135000       Strategy AB      0.00000000        TRUE
## 57 140000 Standard of care 130882.67224310       FALSE
## 58 140000       Strategy AB      0.00000000        TRUE
## 59 145000 Standard of care 141955.86914864       FALSE
## 60 145000       Strategy AB      0.00000000        TRUE
## 61 150000 Standard of care 153029.06605417       FALSE
## 62 150000       Strategy AB      0.00000000        TRUE
## 63 155000 Standard of care 164102.26295971       FALSE
## 64 155000       Strategy AB      0.00000000        TRUE
## 65 160000 Standard of care 175175.45986524       FALSE
## 66 160000       Strategy AB      0.00000000        TRUE
## 67 165000 Standard of care 186248.65677078       FALSE
## 68 165000       Strategy AB      0.00000000        TRUE
## 69 170000 Standard of care 197321.85367631       FALSE
## 70 170000       Strategy AB      0.00000000        TRUE
## 71 175000 Standard of care 208395.05058185       FALSE
## 72 175000       Strategy AB      0.00000000        TRUE
## 73 180000 Standard of care 219468.24748739       FALSE
## 74 180000       Strategy AB      0.00000000        TRUE
## 75 185000 Standard of care 230541.44439292       FALSE
## 76 185000       Strategy AB      0.00000000        TRUE
## 77 190000 Standard of care 241614.64129846       FALSE
## 78 190000       Strategy AB      0.00000000        TRUE
## 79 195000 Standard of care 252687.83820399       FALSE
## 80 195000       Strategy AB      0.00000000        TRUE
## 81 200000 Standard of care 263761.03510953       FALSE
## 82 200000       Strategy AB      0.00000000        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
```



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