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Session 3 - Probabilistic Markov models

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Background

- You've seen how to build deterministic Markov models
- We often don't know transition probabilities, utilities, or costs exactly.
- Best we can do is represent uncertainty around these parameters with probability distributions
- Simulating this uncertainty in economic evaluation models is called **probabilistic analysis**

Not probabilistic sensitivity analysis as the base case itself is uncertain
This is our recommended base case

Outline

- We will adapt the processes and code from the previous session to do the following in probabilistic analysis
- Generating transition matrices
- Generating costs and QALYs
- Markov cohort simulation
- Analysing results

Making transition matrices probabilistic

Probabilistic analysis – transition matrices

- Transition matrix for SoC + website was previously assumed known exactly as

$$\begin{pmatrix} 0.85 & 0.15 \\ 0.08 & 0.92 \end{pmatrix}$$

- In reality, we might estimate this from study data.
- For example, a study of two cohorts of 100 patients followed over 6 months starting in smoking and non-smoking states and receiving standard of care + website.

SoC + website	Smoking at 6 months	Not smoking at 6 months
Smoking at baseline	85	15
Not smoking at baseline	8	92

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Probabilistic analysis – transition matrices

- Binary outcomes data is conveniently represented by a Beta distribution

SoC + website	Smoking at 6 months	Not smoking at 6 months	Distribution
Smoking at baseline	85	15	$Beta\,(85, 15)$
Not smoking at baseline	8	92	$Beta\,(8, 92)$

- If we had more states (e.g. smoking, reduced smoking, no smoking) could use a Dirichlet distribution to represent more than 2 uncertain transition probabilities

Probabilistic analysis – transition matrices

- Each row of the transition matrix for SoC + website is therefore represented by a beta distribution

$$\begin{pmatrix} beta\ (85, 15) \\ beta\ (8, 92) \end{pmatrix}$$

- Similarly, the SoC transition matrix is represented by

$$\begin{pmatrix} beta(88, 12) \\ beta(8, 92) \end{pmatrix}$$

SoC alone	Smoking at 6 months	Not smoking at 6 months	Distribution
Smoking at baseline	88	12	$Beta\ (88, 12)$
Not smoking at baseline	8	92	$Beta\ (8, 92)$

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Probabilistic analysis – beta distribution in R

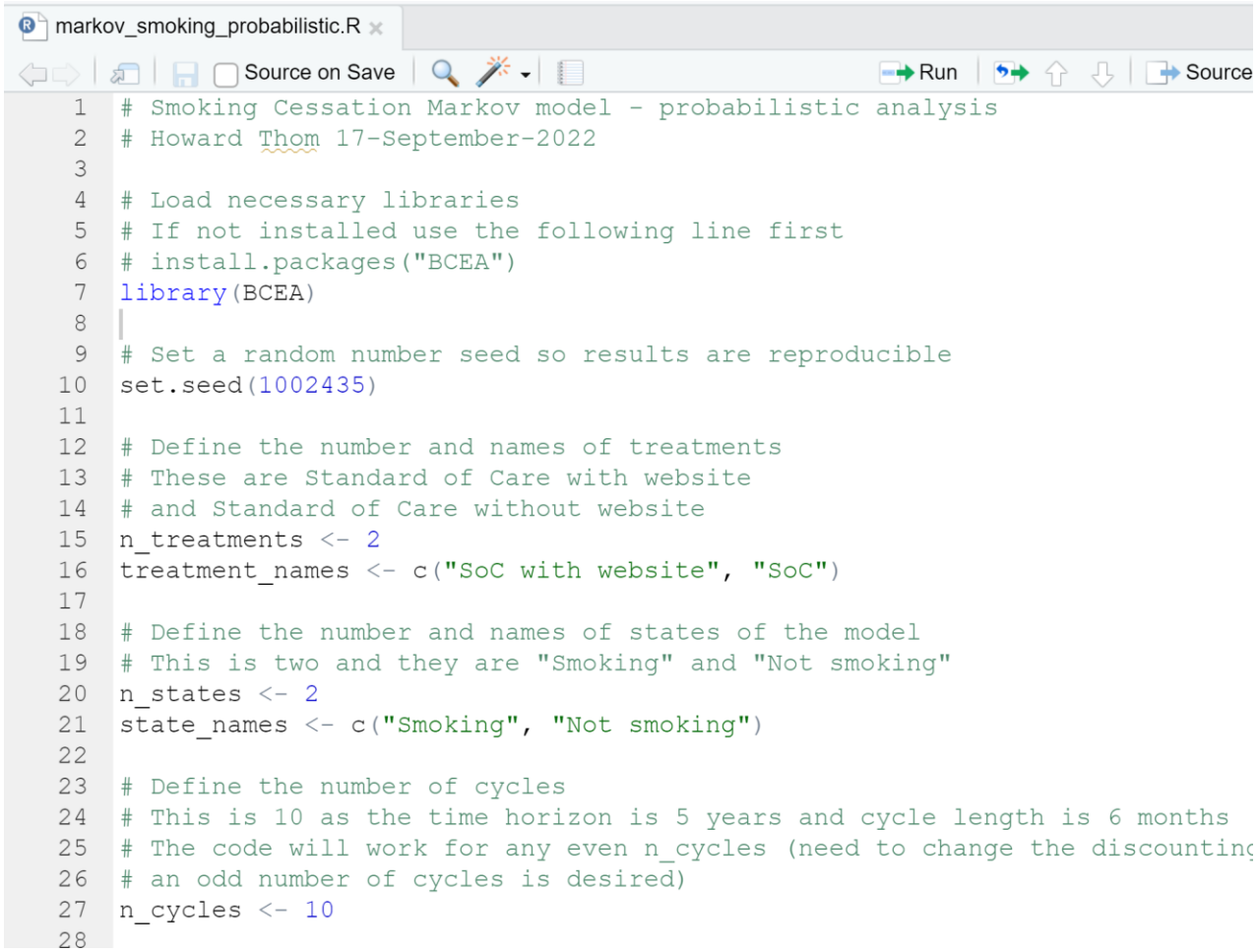
- The `rbeta()` function takes a number of samples 'n' and its α and β parameters

SoC + website	Smoking at 6 months	Not smoking at 6 months	Distribution
Smoking at baseline	85	15	$Beta\,(85, 15)$
Not smoking at baseline	8	92	$Beta\,(8, 92)$

```
> rbeta(n = 10, 85, 15)
 [1] 0.7970600 0.8053360 0.8801466 0.9074958 0.8868830 0.7625788 0.8323798
 [8] 0.8143802 0.8818394 0.8143785
> rbeta(n = 10, 8, 92)
 [1] 0.05580082 0.08638050 0.07016425 0.05184869 0.10193435 0.04942523 0.08096863
 [8] 0.08395457 0.06294023 0.09924210
```

Open the file

- If you haven't already, use R or Rstudio to open the file labelled "markov_smoking_probabilistic.R"
- Note the `set.seed()`
- This ensures results are same each time the model is run, making the analysis reproducible



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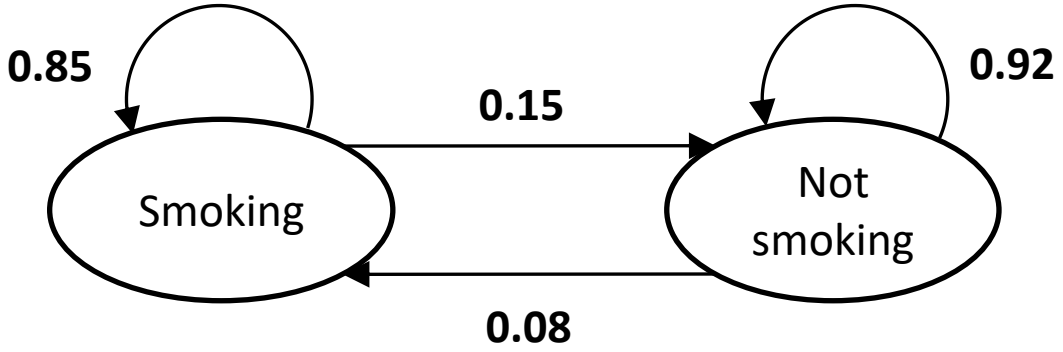
Basic model specification

```
# Define the number and names of treatments
# These are Standard of Care with website
# and Standard of Care without website
n_treatments <- 2
treatment_names <- c("SoC with website", "SoC")

# Define the number and names of states of the model
# This is two and they are "Smoking" and "Not smoking"
n_states <- 2
state_names <- c("Smoking", "Not smoking")

# Define the number of cycles
# This is 10 as the time horizon is 10 years and cycle length is 1 year
# The code will work for any even n.cycles
n_cycles <- 10

# Define simulation parameters
# This is the number of samples to use
n_samples <- 1000
```

An array to store transition matrices




```
# The transition matrix is a 2x2 matrix
# Rows sum to 1
# Top left entry is transition probability from smoking to smoking
# Top right is transition probability from smoking to not smoking
# Bottom left is transition probability from not smoking to smoking
# Bottom right is transition probability from not smoking to not smoking

# There is one transition matrix for each treatment option and each sample
# Store them in an array with (before filling in below) NA entries
transition_matrices <- array(dim = c(n_treatments, n_samples, n_states, n_states),
       dimnames = list(treatment_names, NULL, state_names, state_names))
```

- This produces an array with dimensions 2x1000x2x2
- They are currently blank so need to fill in with values…

Filling in the transition matrix

```
# First the transition matrix for Standard of Care with website
# Transitions from smoking
temp <- rbeta(n_samples, 85, 15)
transition_matrices["SoC with website", , "Smoking", ] <-
                                matrix(c(temp, 1 - temp), ncol = 2)
# Transitions from not smoking
temp <- rbeta(n_samples, 8, 92)
transition_matrices["SoC with website", , "Not smoking", ] <-
                                matrix(c(temp, 1 - temp), ncol = 2)

# Second the transition matrix for Standard of Care
# Transitions from smoking
temp <- rbeta(n_samples, 88, 12)
transition_matrices["SoC", , "Smoking", ] <- matrix(c(temp, 1-temp), ncol = 2)
# Transitions from not smoking
# These should be the same as the transition probabilities from not smoking for SoC with website
# as the website has no impact on probability of relapse
transition_matrices["SoC", , "Not smoking", ] <-
                                transition_matrices["SoC with website", , "Not smoking", ]
```

Contents of array?

- Run the code up to line 64, ensuring you have filled in the transition matrices array
- Look at elements of the array
- For example, first sampled transition matrix for standard of care.
- But note that these are random samples so won't match the means.

```
> transition_matrices["SoC", 1, ,]
                Smoking Not smoking
Smoking       0.8568441   0.1431559
Not smoking   0.1053515   0.8946485
```

Contents of array?

- Or the 10th sample for standard of care with website
- Or first 10 samples of transition probabilities from ‘Smoking’ on standard of care with website

```
> transition_matrices["SoC", 10, ,]
               Smoking Not smoking
Smoking     0.87416988   0.1258301
Not smoking 0.07119714   0.9288029
> transition_matrices["SoC", 1:10, "Smoking" ,]
         Smoking Not smoking
 [1,] 0.8568441   0.1431559
 [2,] 0.8696609   0.1303391
 [3,] 0.8373699   0.1626301
 [4,] 0.8784279   0.1215721
 [5,] 0.8927902   0.1072098
 [6,] 0.8735486   0.1264514
 [7,] 0.8843967   0.1156033
 [8,] 0.8617107   0.1382893
 [9,] 0.8109626   0.1890374
[10,] 0.8741699   0.1258301
```

Exercise 1

a) Run the code as far as line 64 to fill in the transition matrices array.

b) One sample of the transition probabilities from Smoking on SoC with website are given by calling

```
transition_matrices["SoC with website", 1, "Smoking", ]
```

Use the `colMeans()` function to compare the average over all samples of the transition probabilities from Smoking to Smoking and Not smoking on SoC with website and SoC.

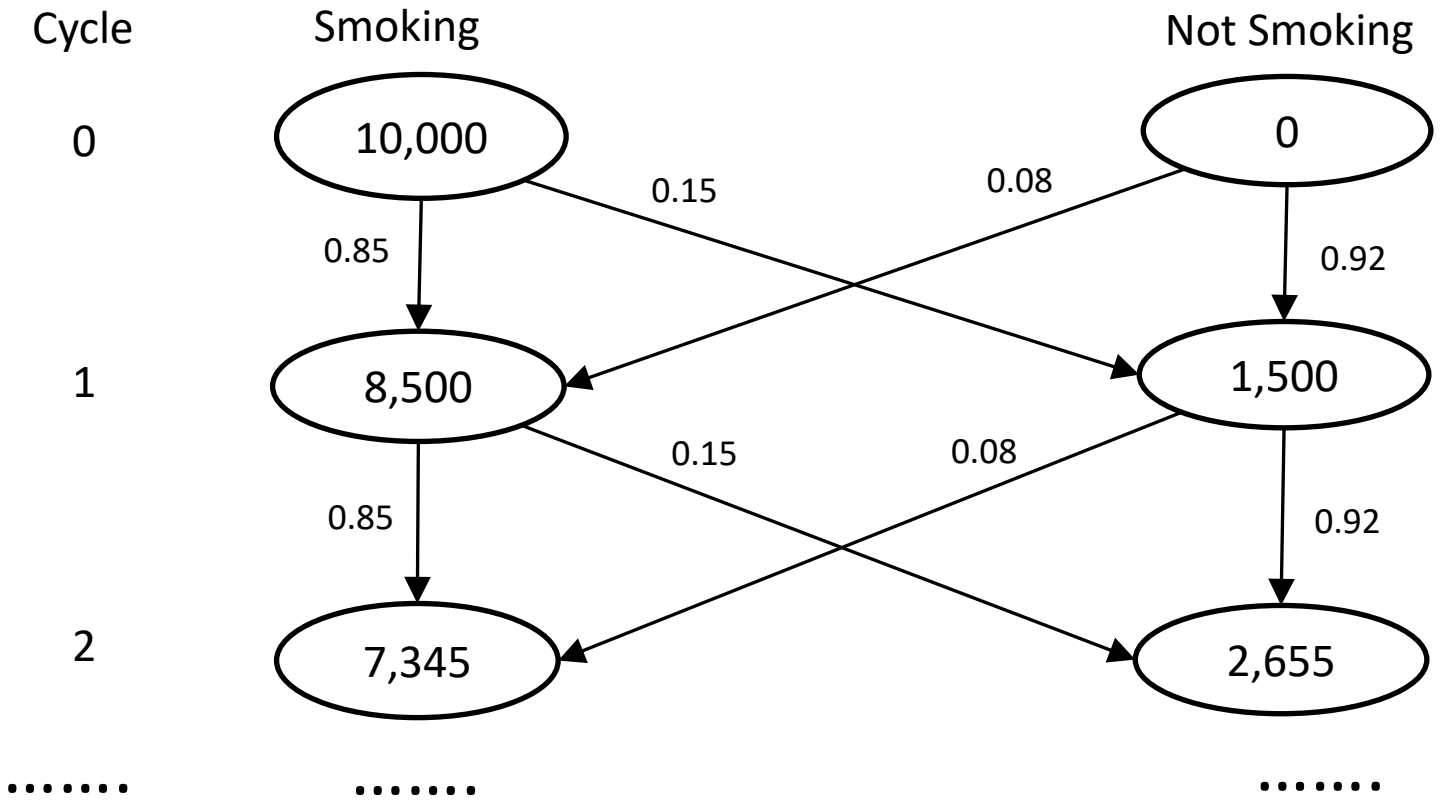
c) What about the transition probabilities from not smoking? Do they differ between SoC with website and SoC alone?

Markov simulation in probabilistic analysis

Reminder: Cohort Simulation

- Cohort vector π at time t (π_t) is the cohort vector at the previous time point (π_{t-1}) multiplied by the probability transition matrix P

$$\pi_t = \pi_{t-1}P$$



Initialise the cohort vector

```
# Build an array to store the cohort vector at each cycle
# Each cohort vector has 2 (=n_states) elements: probability of being in smoking state,
# and probability of being in the not smoking state
# There is one cohort vector for each treatment, for each sample, for each cycle.
cohort_vectors <- array(dim = c(n_treatments, n_samples, n_cycles,
n_states), dimnames = list(treatment_names, NULL, NULL, state_names))

# Assume that everyone starts in the smoking state no matter the treatment
cohort_vectors[, , 1, "Smoking"] <- 1
cohort_vectors[, , 1, "Not smoking"] <- 0
```

- These are the two-dimensional π_t in the Markov formula

Core loop

Loop over treatments

{

Loop over samples

{

Loop over cycles

{

Update cohort vector

$$\pi_t = \pi_{t-1}P$$

or specifically…

$$(\pi_{Smoking,t}, \pi_{Not\ smoking,t}) = (\pi_{Smoking,t-1}, \pi_{Not\ smoking,t-1})P$$

}

1. Calculate cycle costs and QALYs for this sample
2. Calculate total costs and QALYs for this sample

}

}

Core loop

```
# Loop over the treatment options
for (i_treatment in 1:n_treatments)
{
        # Loop over the samples
        for (i_sample in 1:n_samples)
        {
                # Loop over the cycles
                # Cycle 1 is already defined so only need to update cycles 2:n_cycles
                for (i_cycle in 2:n_cycles)
                {
                        # Multiply previous cycle's cohort vector by transition matrix
                                cohort_vectors[i_treatment, i_sample, i_cycle, ] <-
                                cohort_vectors[i_treatment, i_sample, i_cycle-1, ] %*%
                                transition_matrices[i_treatment, i_sample, , ]
                }               }
                1. Calculate cycle costs and QALYs for this sample
                2. Calculate total costs and QALYs for this sample
        }
}
```

Core loop

```
# Loop over the treatment options
for (i_treatment in 1:n_treatments)
{
        # Loop over the samples
        for (i_sample in 1:n_samples)
        {
                # Loop over the cycles
                # Cycle 1 is already defined so only need to update cycles 2:n_cycles
                for (i_cycle in 2:n_cycles)
                {
                        # Multiply previous cycle's cohort vector by transition matrix
                                cohort_vectors[i_treatment, i_sample, i_cycle, ] <-
                                cohort_vectors[i_treatment, i_sample, i_cycle-1, ] %*%
                                transition_matrices[i_treatment, i_sample, , ]
                }                       }
                1. Calculate cycle costs and QALYs for this sample
                2. Calculate total costs and QALYs for this sample
        }
}
```

This will be implemented next

Making costs and QALYs probabilistic

Probabilistic sensitivity analysis – costs and QALYs

- The QALYs associated with 1 year in the smoking state are now normally distributed as Normal(mean = 0.95, sd = 0.01)
- The QALYs associated with 1 year in the non-smoking state remain fixed at 1.00 (perfect health)
- Cost of website also remains fixed as £50

State QALYs

```
# Now define the QALYS associated with the states per cycle
# There is one for each sample and each state
# Store in an NA array and then fill in below
state_qalys <- array(dim = c(n_samples, n_states), dimnames = list(NULL,
state_names))

# QALY associated with 1-year in the smoking state is Normal(mean=0.95, SD=0.01)
state_qalys[, "Smoking"] <- rnorm(n_samples, mean=0.95, sd=0.01)

# QALY associated with 1-year in the not smoking state is 1 (no uncertainty)
# So all samples have the same value
state_qalys[, "Not smoking"] <- 1
```

State costs

```
# And finally define the state costs
# These are all zero as the only cost is a one-off subscription fee of £50
# to the smoking cessation website
state_costs <- array(0, dim = c(n_samples, n_states), dimnames = list(NULL,
state_names))
```

- Can again inspect elements to make sure it's working as expected…

Checking state costs and QALYs

```
> state_qalys[1:5, "Smoking"]
[1] 0.9456194 0.9502963 0.9525456 0.9536680 0.9423465
> state_qalys[1:5, "Not smoking"]
[1] 1 1 1 1 1
> state_costs[1:5, "Smoking"]
[1] 0 0 0 0 0
> state_costs[1:5, "Not smoking"]
[1] 0 0 0 0 0
```

- State QALYs in smoking state are uncertain but centred around 0.95
- QALYs in not smoking state are 1
- And state costs are always zero

Treatment costs

```
# Define the treatment costs
# One for each  sample and each treatment
# Treatment costs are actually fixed but this allows flexibility if we
# want to include uncertainty/randomness in the cost
treatment_costs <- array(dim = c(n_treatments, n_samples), dimnames = list(treatment_names,
NULL))

# Cost of the smoking cessation website is a one-off subscription fee of £50
treatment_costs["SoC with website", ] <- 50
# Zero cost for standard of care
treatment_costs["SoC", ] <- 0
```

Cycle costs and cycle QALYs

```
# Build an array to store the costs and QALYs accrued per cycle
# One for each treatment, for each  sample, for each cycle
# These will be filled in below in the main model code
# Then discounted and summed to contribute to total costs and total QALYs
cycle_costs <- array(dim = c(n_treatments, n_samples, n_cycles),
       dimnames = list(treatment_names, NULL, NULL))
cycle_qalys <- array(dim = c(n_treatments, n_samples, n_cycles),
       dimnames = list(treatment_names,NULL, NULL))
```

- Not strictly necessary to store these but might be interested in costs or QALYs accrued per cycle.

Arrays to store total cost and QALYs

```
# Build arrays to store the total costs and total QALYs
# There is one for each treatment and each  sample
# These are filled in below using cycle_costs,
# treatment_costs, and cycle_qalys
total_costs <- array(dim = c(n_treatments, n_samples),
      dimnames = list(treatment_names, NULL))
total_qalys <- array(dim = c(n_treatments, n_samples),
      dimnames = list(treatment_names,NULL))
```

- Once filled in by Markov loop, these are used to calculate net benefit and ICERs

Calculating cycle costs and QALYs

- For each treatment and each sample, we use the cohort_vectors[] to calculate costs and QALYs associated with each cycle

```
# Now use the cohort vectors to calculate the total costs for each cycle
cycle_costs[i_treatment, i_sample, ] <- cohort_vectors[i_treatment, i_sample, , ]
%*% state_costs[i_sample, ]

# And total QALYs for each cycle
cycle_qalys[i_treatment, i_sample, ] <- cohort_vectors[i_treatment, i_sample, , ]
%*% state_qalys[i_sample, ]
```

Core loop

```
# Loop over the treatment options
for (i_treatment in 1:n_treatments)
{
        # Loop over the  samples
        for (i_sample in 1:n_samples)
        {
                # Loop over the cycles
                # Cycle 1 is already defined so only need to update cycles 2:n_cycles
                for (i_cycle in 2:n_cycles)
                {
                        # Multiply previous cycle's cohort vector by transition matrix
                        # i_e_ pi_j = pi_(j-1)*P
                        cohort_vectors[i_treatment, i_sample, i_cycle, ] <-
                                cohort_vectors[i_treatment, i_sample, i_cycle-1, ] %*%
                                transition_matrices[i_treatment, i_sample, , ]
                }
# Now use the cohort vectors to calculate the total costs for each cycle
cycle_costs[i_treatment, i_sample, ] <- cohort_vectors[i_treatment, i_sample, , ] %*% state_costs[i_sample, ]
# And total QALYs for each cycle
cycle_qalys[i_treatment, i_sample, ] <- cohort_vectors[i_treatment, i_sample, , ] %*% state_qalys[i_sample, ]

        2. Calculate total costs and QALYs for this  sample
        }
}
```

Implement this final step in R

Calculating total costs and QALYs

```
# Combine the cycle_costs and treatment_costs to get total costs
# Apply the discount factor
# (1 in first year, 1_035 in second, 1_035^2 in third, and so on)
total_costs[i_treatment, i_sample] <- treatment_costs[i_treatment, i_sample]
+ cycle_costs[i_treatment, i_sample, ] %*% (1 / 1.035)^c(0:(n_cycles - 1))

# Combine the cycle_qalys to get total qalys
# Apply the discount factor
# (1 in first year, 1_035 in second, 1_035^2 in third, and so on)
total_qalys[i_treatment, i_sample] <- cycle_qalys[i_treatment, i_sample, ]
%*% (1 / 1.035)^c(0:(n_cycles - 1))
```

- Note treatment costs are added (and not discounted as only occur in first year)

Analysing results in probabilistic analysis

Mean costs and effects

```
# Average costs
# These are £50 on the website and 0 on standard of care as there are no costs other than the website subscription cost
average_costs <- rowMeans(total_costs)
# Average effects (in QALY units)
# These are slightly higher on the website as higher probability of quitting smoking
average_effects <- rowMeans(total_qalys)
```

```
> average_costs
SoC with website             SoC
              50               0
> average_effects
SoC with website             SoC
        8.335657        8.312823
```

- So we see that costs are higher on website (knew that!) but that QALYs are also higher

Incremental Cost-Effectiveness Ratio

```
# Incremental costs and effects relative to standard of care
# No uncertainty in the costs as the website cost is fixed at £50
incremental_costs <- total_costs["SoC with website", ] - total_costs["SoC", ]

# In some samples the website leads to higher QALYs but in others it is negative
# There is uncertainty as to whether the website is an improvement over SoC
incremental_effects <- total_qalys["SoC with website", ] - total_qalys["SoC", ]

# The ICER comparing Standard of care with website to standard of care
# This is much lower than the £20,000 willingness-to-pay threshold indicating good value for money
ICER <- mean(incremental_costs) / mean(incremental_effects)
```

```
> ICER
[1] 2189.675
```

- Website likely cost-effective

Incremental net benefit

```
incremental_net_benefit <- 20000*incremental_effects - incremental_costs
```

```
> incremental_net_benefit[1:25]
 [1]   -66.63142  -572.28912 -1156.38185  -126.22416   329.89004    85.92978  -330.26905
 [8]   375.96309  -989.76463   145.49691   -54.96843   299.97584   175.68669  1157.99548
[15]   179.79911   -48.40267   540.35523   760.72917   957.34924  1022.26724  1107.25053
[22]  -317.20661   288.24832   774.12674  1478.91898
```

- This is sometimes positive and sometimes negative
- Need to look at the average to get a clearer picture

```
> average_inb <- mean(incremental_net_benefit)
> average_inb
[1] 406.6887
```

- Positive so expected net benefit higher on website than on standard of care

Probability cost-effective

```
> probability_cost_effective <- sum(incremental_net_benefit > 0) / n_samples
> probability_cost_effective
[1] 0.711
```

- This is the proportion of samples for which the incremental net benefit is positive
- It is close to 71%, representing good degree of certainty in recommendation to adopt the smoking cessation website

Analysing the results using BCEA

- BCEA (Bayesian Cost Effectiveness Analysis) is a package to analyse the results (simulated total costs and total QALYs) and produce standard output such as ICERs, CEACs and EVPI.

Note: In this example can't use total_costs and total_qalys directly in BCEA as they are n_treatments by n_samples rather than n_samples by n_treatments. Use the t() function to transpose the total_costs and total_qalys matrices when inputting them to BCEA.

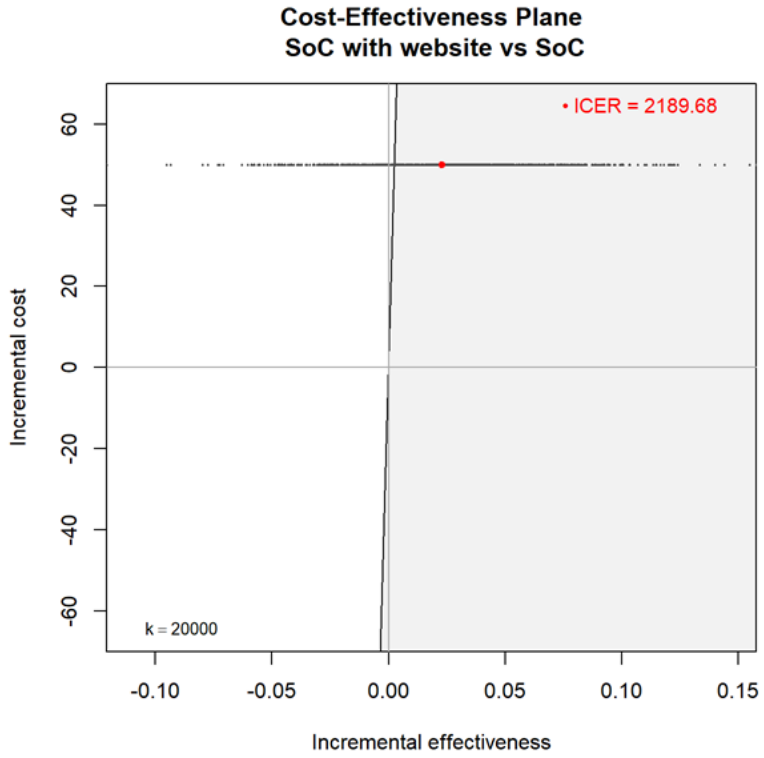
```
Smoking_bcea <- bcea(e = t(total_qalys), c = t(total_costs), ref = 1,
interventions = treatment_names)

summary(smoking_bcea, wtp = 20000)
```

BCEA output

```
Cost-effectiveness analysis summary

Reference intervention:  SoC with website
Comparator intervention: SoC

Optimal decision: choose SoC for k < 2200 and SoC with website for k >= 2200


Analysis for willingness to pay parameter k = 20000

                 Expected net benefit
SoC with website                166663
SoC                             166256

                            EIB  CEAC   ICER
SoC with website vs SoC 406.69 0.711 2189.7

Optimal intervention (max expected net benefit) for k = 20000: SoC with website

EVPI 135.06
```

Cost-effectiveness plane

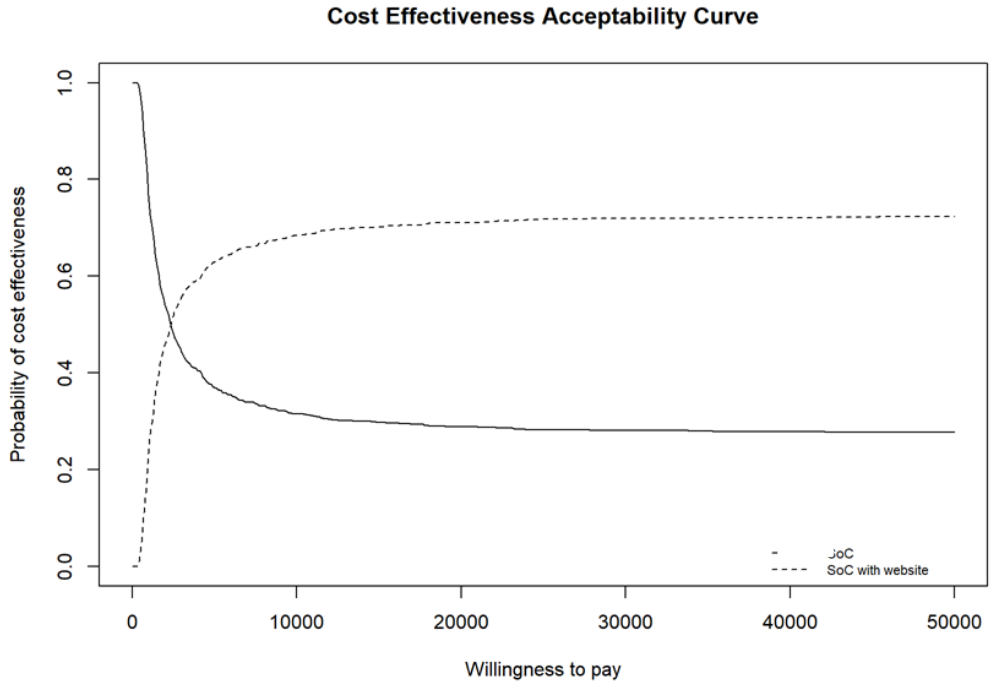
```
ceplane.plot(smoking_bcea, wtp = 20000, ylim = c(-70, 70))
```



- We chose the y (cost) limits manually to capture all points.
- Cost differential is always £50 as cost of website is fixed
- Variation in effectiveness over simulated sample plotted

Cost Effectiveness Acceptability Curve

```
smoking_multi_ce <- multi.ce(smoking_bcea)
ceac.plot(smoking_multi_ce)
```



- SoC is optimal up to £2200 willingness-to-pay per QALY
- Above £2300 SoC with website is optimal

Summary

- We have explained key steps in building both deterministic and probabilistic discrete-time cohort Markov models
- To make a model probabilistic we need to
  - Sample probabilistic transition matrices
  - Simulate the Markov model using these probabilistic matrices
  - Sample probabilistic state costs and QALYs
  - Analyse the results accounting for uncertainty in costs, QALYs, and net benefits
- The code we provided is general
  - For example, included state costs even though these are zero in smoking cessation

Exercise 2 – Adding a death state

In reality, models will have more than two states.

Go through the code and add in an extra state to represent death by:

a) Change number of states from 2 to 3 and naming the death state
b) Assume that there are 2 deaths in every 100 patients in the smoking state and 1 death in the non-smoking state, each represented by a beta distribution. **(See next slide for hint on implementation using two beta distributions)**
c) Define transitions from death so that it is an absorbing state that people cannot move back from.
d) Check that you have set up your transition matrix correctly using the code transition_matrices["SoC with website", 1, ,]
e) Assign a QALY of 0 and a cost of 0 to the death state
f) Rerun the simulation including the death state, assuming that no one starts in the death state
g) Analyse the results using BCEA. What impact does adding the death state have on the results?

Exercise 2 – Transitions using two beta distributions

```
# Assume that people have a 2/100 probability of dying in the smoking state
# and a 1/100 probability of dying in the non-smoking state.
probability_of_death_smoking <- rbeta(n_samples, 2, 98)
probability_of_death_not_smoking <- rbeta(n_samples, 1, 99)

# Transitions from smoking
temp <- rbeta(n_samples, 85, 15)
transition_matrices["SoC with website", , "Smoking", ] <-
matrix(c((1 - probability_of_death_smoking) * c(temp, 1 - temp),
probability_of_death_smoking), ncol = 3)
```

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Exercise 2 – Solution

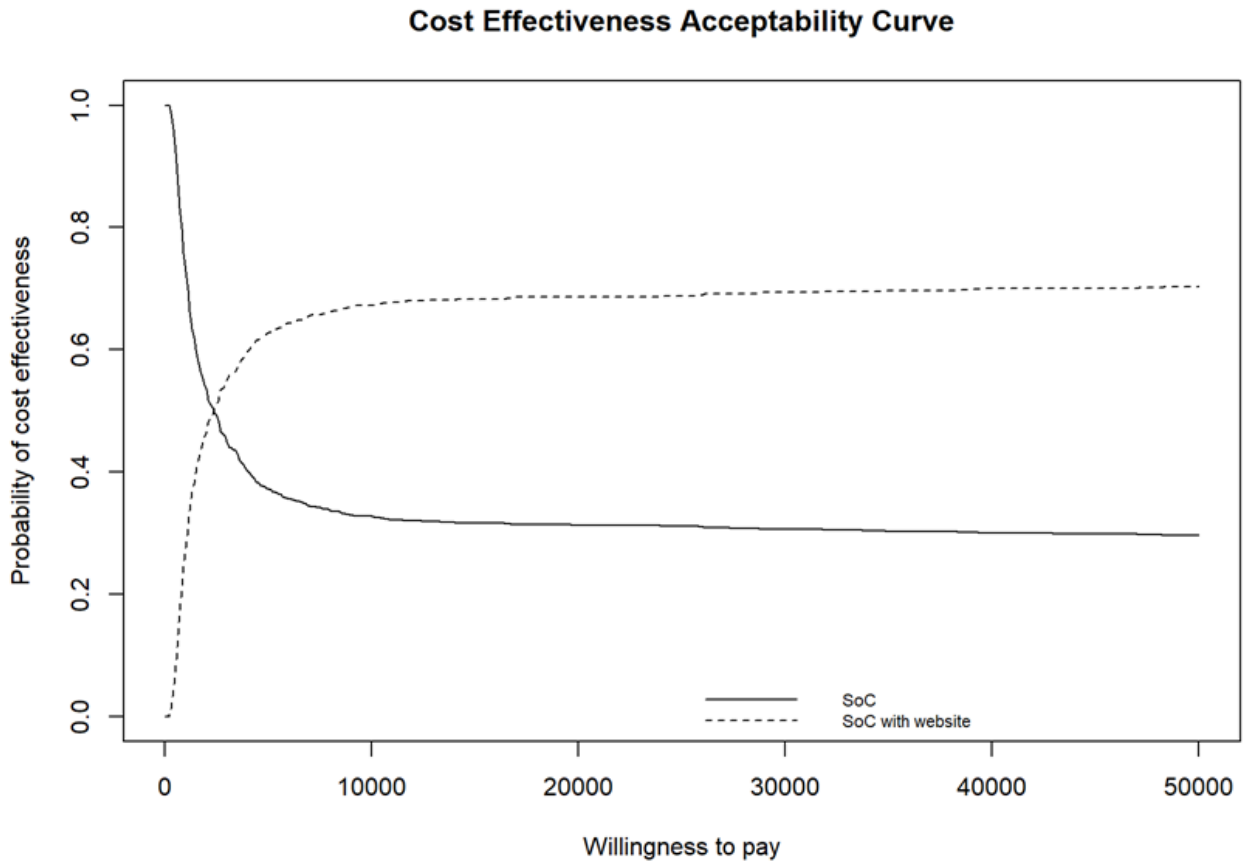
Using summary() of the new bcea object should give

	EIB	CEAC	ICER
SoC with website vs SoC	470.31	0.687	1921.9

The ICER is marginally reduced (from 2189.7) because the difference in effects is increased.

Uncertainty is marginally increased as CEAC has gone from 0.711 to 0.676, so closer to 0.50.

Code in session_3_exercise_2_solution.R



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Thank you!

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