Conducting model-based cost-effectiveness analyses:
A tutorial

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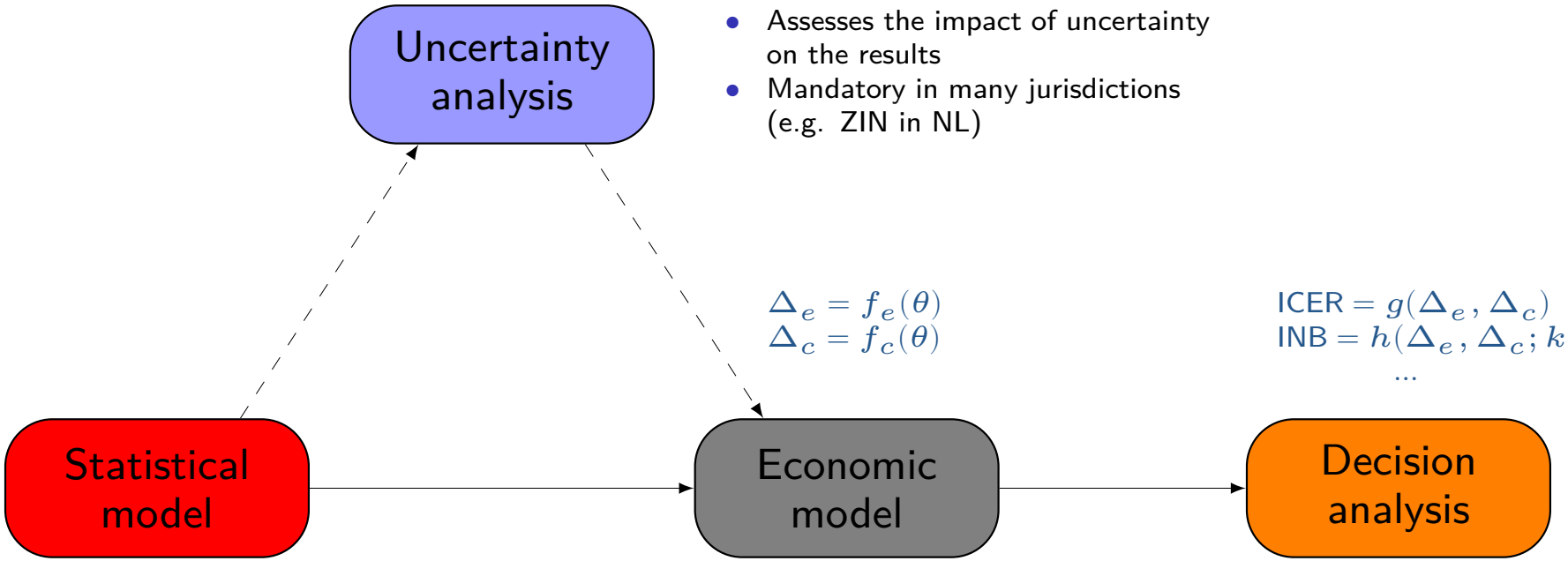
Section 1

Introduction & Modelling in HTA

Health technology assessment (HTA)

- **Objective**: Combine costs & benefits of a given intervention into a rational scheme for allocating resources



- Assesses the impact of uncertainty on the results
- Mandatory in many jurisdictions (e.g. ZIN in NL)

- Estimates relevant parameters θ
- Varies with the type of data (& statistical approach!)

- Combines parameters to obtain average measure for costs and effects
- Varies with the type of data & statistical model used

- Computes suitable measures of "cost-effectiveness"
- Dictates the best course of actions
- Standardised process

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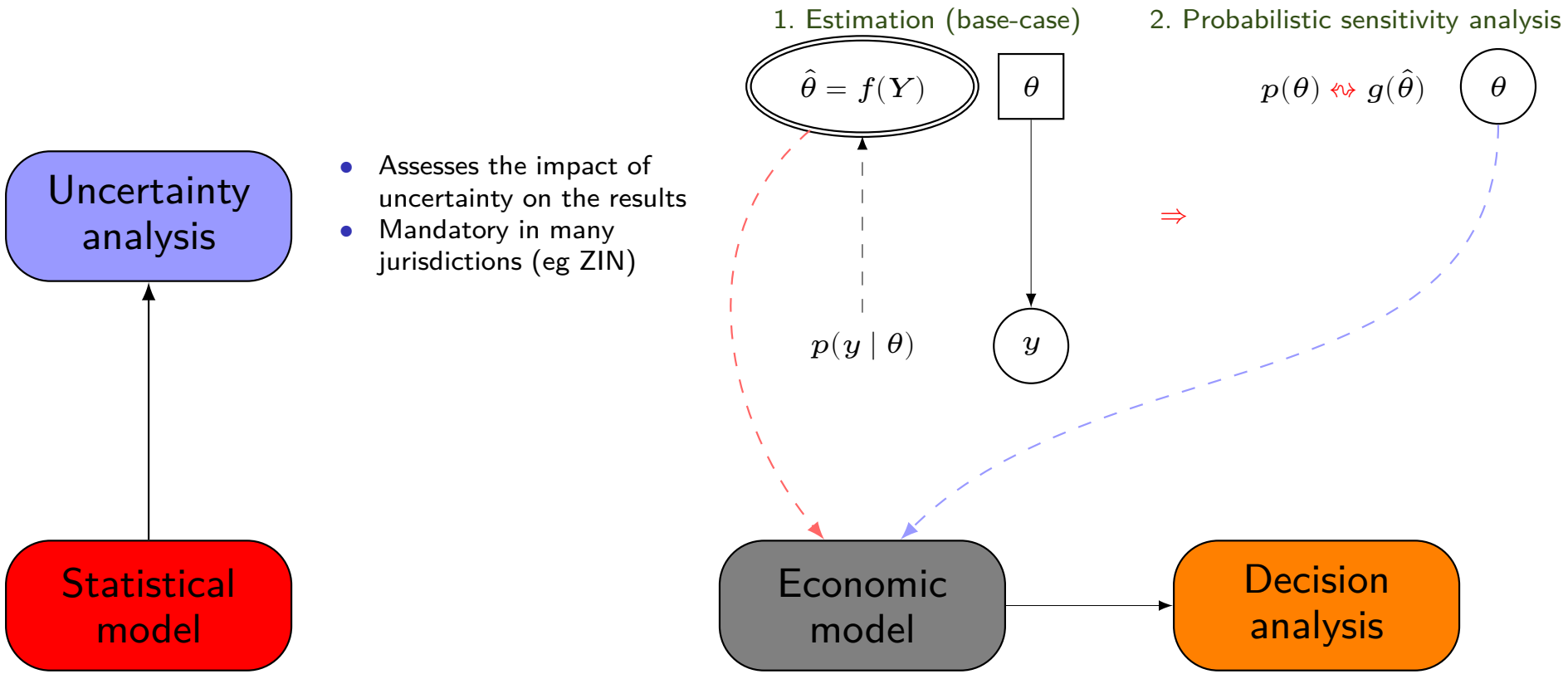
"Two-stage" approach to HTA



- Assesses the impact of uncertainty on the results
- Mandatory in many jurisdictions (eg ZIN)

- Estimates relevant parameters θ
- Varies with the type of data (& statistical approach!)

- Combines the parameters to obtain a population average measure for costs and effects
- Varies with the type of data & statistical model used

- Computes suitable measures of "cost-effectiveness"
- Dictates the best course of actions
- Standardised process

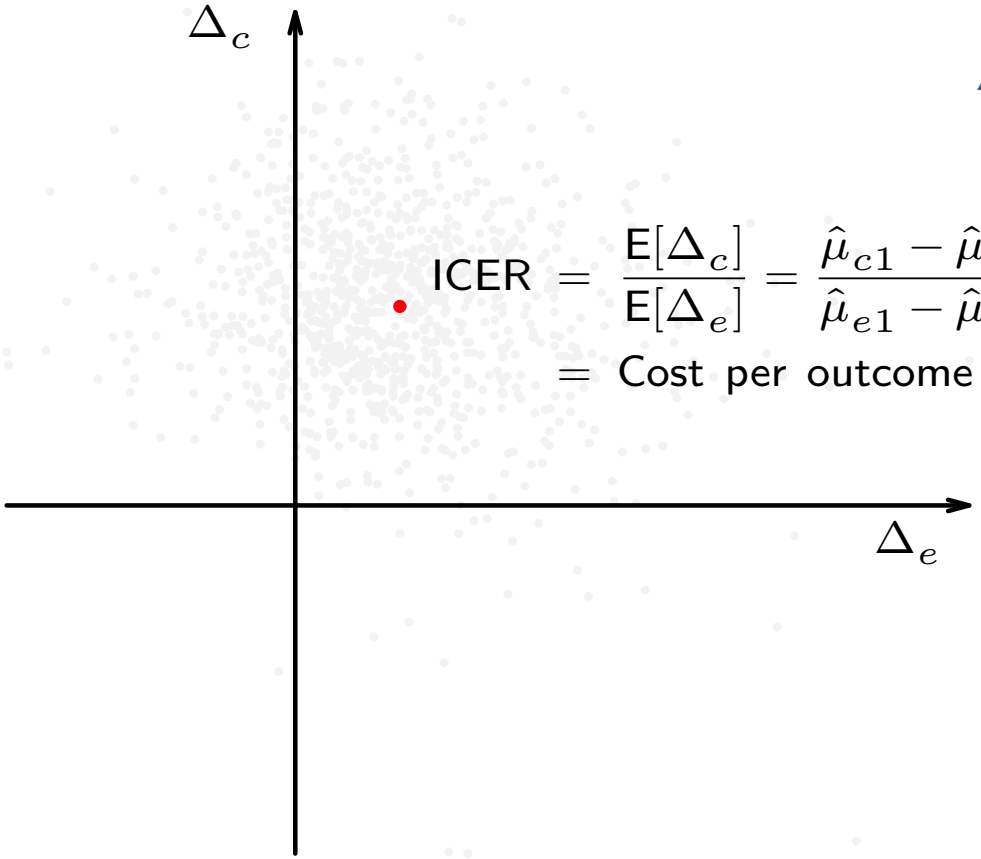
"Two-stage approach" (Spiegelhalter, Abrams & Myles, 2004)

Decision + Uncertainty* analysis

Cost-effectiveness plane

$$\Delta_e = \underbrace{\mathsf{E}[e \mid \hat{\theta}_1]}_{\hat{\mu}_{e1}} - \underbrace{\mathsf{E}[e \mid \hat{\theta}_0]}_{\hat{\mu}_{e0}}$$

$$\Delta_c = \underbrace{\mathsf{E}[c \mid \hat{\theta}_1]}_{\hat{\mu}_{c1}} - \underbrace{\mathsf{E}[c \mid \hat{\theta}_0]}_{\hat{\mu}_{c0}}$$



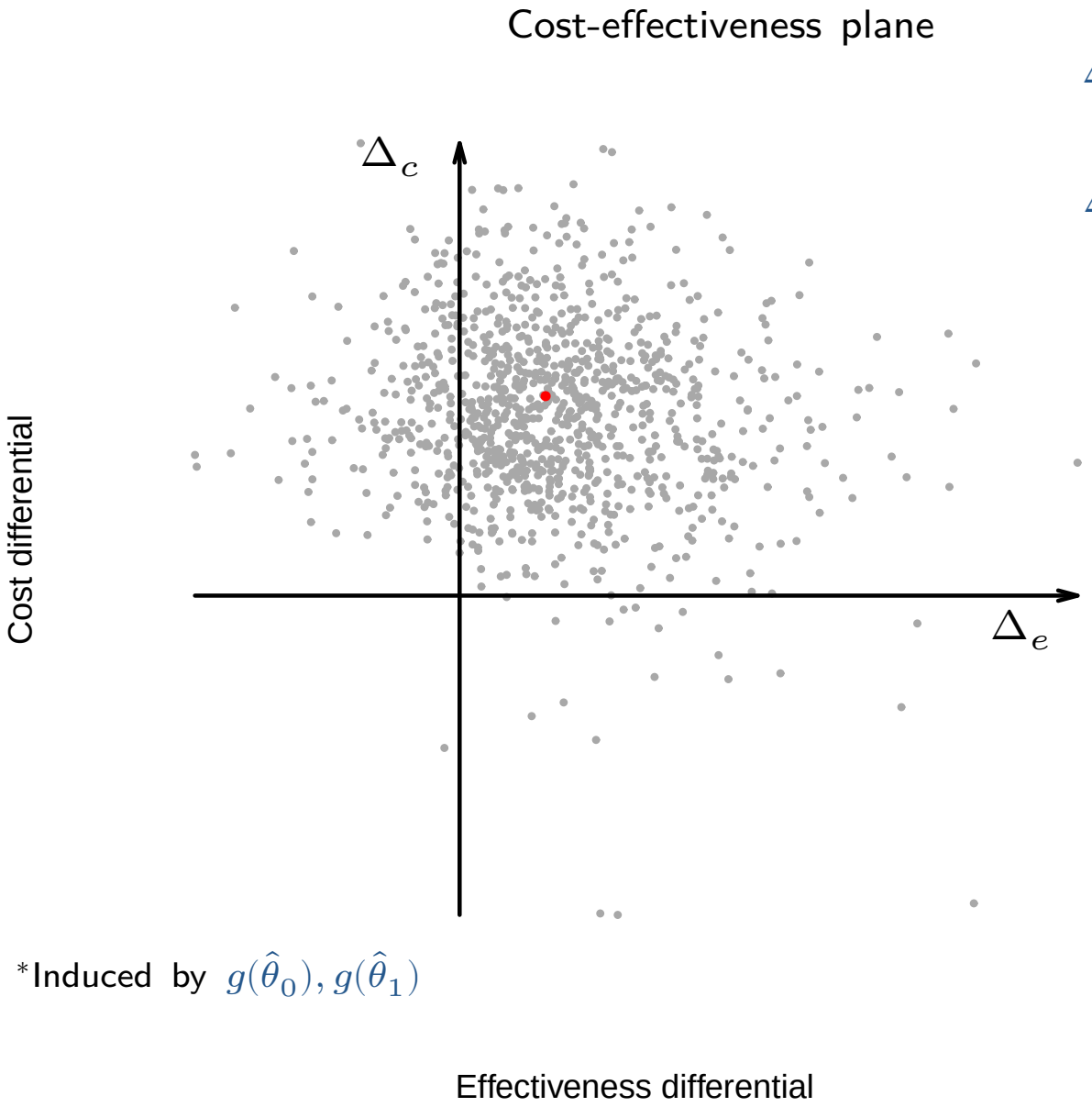
$$\text{ICER} = \frac{\mathsf{E}[\Delta_c]}{\mathsf{E}[\Delta_e]} = \frac{\hat{\mu}_{c1} - \hat{\mu}_{c0}}{\hat{\mu}_{e1} - \hat{\mu}_{e0}}$$

$$= \text{Cost per outcome}$$

Cost differential

Effectiveness differential

Decision + Uncertainty* analysis



$$\Delta_e = \underbrace{\mathsf{E}[e \mid \theta_1]}_{\mu_{e1}} - \underbrace{\mathsf{E}[e \mid \theta_0]}_{\mu_{e0}}$$

$$\Delta_c = \underbrace{\mathsf{E}[c \mid \theta_1]}_{\mu_{c1}} - \underbrace{\mathsf{E}[c \mid \theta_0]}_{\mu_{c0}}$$

*Induced by $g(\hat{\theta}_0), g(\hat{\theta}_1)$

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Section 2

Zorginstituut Nederland (ZIN) 2024 guidelines

ZIN 2024 guidelines: summary

- Cost-effectiveness in the Netherlands has become more and more important in reimbursement decisions of the *National Health Care Institute* over the years
- **Standardise** analyses to improve comparability and enhance quality
- Revision of elements for the "**Reference Case**" to which all economic evaluations *have to comply with*
  1. **Perspective** of the analysis
  2. **PICOTS** criteria
  3. **Type** of evaluation
  4. **Data** (effectiveness, costs and QoL)
  5. **Methods**
     - **MB**: Discount, Extrapolation, Subgroup, Uncertainty, Validation
     - EMP: Missingness, Adjustment, Uncertainty

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  6. **Reporting**
     - **Data**, **Methods**, **Results**

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Analysis Methods in HTA

- **Study Design**:
  - Empirical - *costs & effects at patient level from a controlled study*
  - **Model-based** - *expected costs & effects estimated via simulation*

Analysis Methods in HTA

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  - In simulation, choice of **model type and inputs** should be based on the *research question* and *nature of the disease*
- Focus on **recommended methods** in the context of a *homogeneous population*:
  - No *systematic literature review* needed
  - Annual *discounting* for costs at 3% & effects at 1.5%
  - Model *evidence* come from randomised controlled trails
  - *Extrapolation* based on parametric distributions
  - No *subgroup* or *Value of Information* analysis
  - No *validation* of source data

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Types of model-based analyses (Caro et al. 2012)

- **Decision-tree models**
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Section 3

Popular Decision-Analytic Models in HTA

Decision Trees

- Use to graphically display a **tree structure**:
  - Alternative possibilities as **branches**
  - **Distinct**and **mutually exclusive**

Decision Trees

- Use to graphically display a **tree structure**:
  - Alternative possibilities as **branches**
  - **Distinct**and **mutually exclusive**
- Branches are connected together through different types of **Nodes**:
  - **Decision**→ root of the tree (eg alternative trt choices)
  - **Chance**→ probability of event occurrence (eg success/failure)
  - **Terminal**→ given "value" (eg cost/benefit)

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- At each node, probabilities p_j of an event x_j given a past event x_i:
  - are **conditional** probabilities → $p_j = p(x_j \mid x_i)$
  - must sum up to one

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Decision Trees

- **Example**:
  - Two treatments are compared to no treatment (None, A, B)
  - Each has costs/benefits v_j in terms of p_j of being successful

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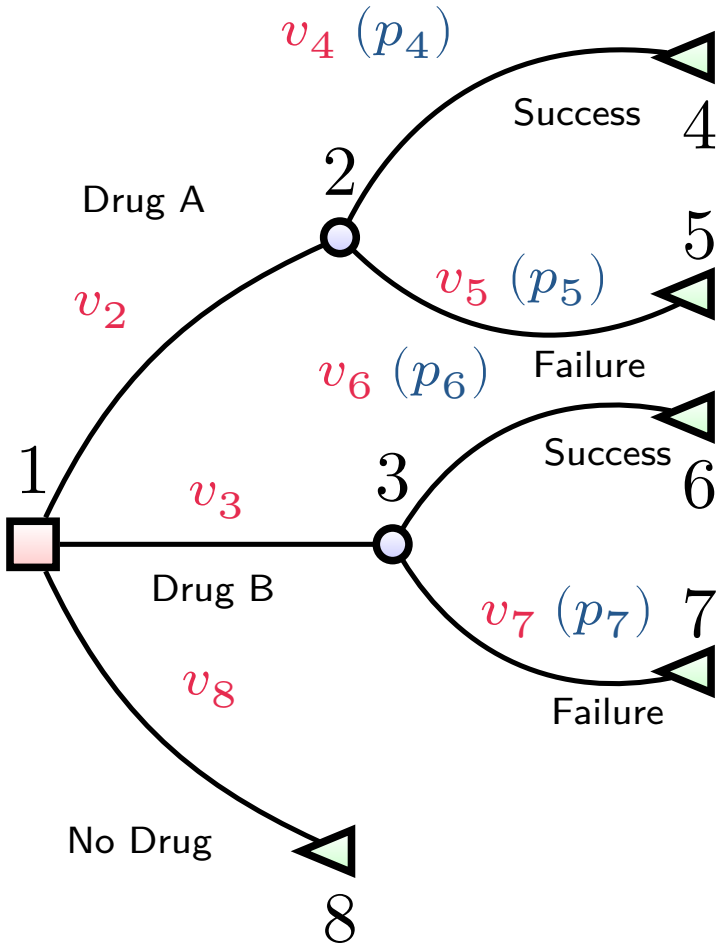

Decision Trees

- Decision trees are used due to their **simplicity** to:
  - Describe disease natural history and treatment outcomes
  - Quantify the **risks**/payoffs associated with different courses of action
  - Show alternative clinical pathways where **discrete decisions** and related **payoffs** occur in sequence in short time frames

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  - Describe disease natural history and treatment outcomes
  - Quantify the **risks**/payoffs associated with different courses of action
  - Show alternative clinical pathways where **discrete decisions** and related **payoffs** occur in sequence in short time frames
- But they have quite a few **limitations** :
  - Not suited for simulations with large gaps between **decisions** and **realisation** of the payoffs
  - Influence of **time** cannot be easily incorporated
  - Difficult to incorporate the **chance of returning** to past nodes (eg recovery from illness)

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Decision Trees - computation

- Calculation of expected **costs**/**benefits** values of *terminal nodes* based on $p(x_j \mid x_i)$
- Think of a unique pathway from root ($x_{[1]}$) until terminal node ($x_{[n]}$)

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Decision Trees - computation

- Calculation of expected **costs**/**benefits** values of *terminal nodes* based on $p(x_j \mid x_i)$
- Think of a unique pathway from root ($x_{[1]}$) until terminal node ($x_{[n]}$)
- Chaining $p(x_j \mid x_i)$ for a given pathway gives the **joint probability** of reaching the terminal node

$$p(x_{[1]}, \dots, x_{[n]}) = p(x_{[2]} \mid x_{[1]}) \times \cdots \times p(x_{[n]} \mid x_{[n-1]}) = \prod_{i=1}^{n-1} p(x_{[i+1]} \mid x_{[i]})$$

- Associated **costs**/**benefits** values are the respective sets of payoffs $v = (v_{[1]} = (c_{[1]}, e_{[1]}), \dots, v_{[n]} = (c_{[n]}, e_{[n]}))$

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Decision Trees - computation

- **Backwards computation**
  - weighted average of the **total values** of the successive (**child**) nodes of a given past (**parent**) node
  - **weights** = probability to go through each branch to the **child** nodes
  - starting at the **terminal nodes** the expected values at each **chance node** is calculated in turn all the way back to the **decision node**

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  - calculate **total values** and **joint probabilities** along all of the distinct pathways of the tree corresponding to a decision
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- **Forward computation**
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  - weighted average of values & probabilities gives the expected value at the **decision node**
- Expected outcomes often expressed in terms of **incremental means** between two competing treatments for some
  - **benefit measure** (eg QALYs) $\Delta_e = \mathsf{E}[e \mid \mathrm{trt}_2] - \mathsf{E}[e \mid \mathrm{trt}_1]$
  - **costs** $\Delta_c = \mathsf{E}[c \mid \mathrm{trt}_2] - \mathsf{E}[c \mid \mathrm{trt}_1]$

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Decision Trees - forward computation

- Assign **values** to each terminal node $v_j = (e_j, c_j)$
  - trt $= 1$: $e_j = (e_{\mathsf{S}} = 35, e_{\mathsf{F}} = 15)$, $c_j = (c_{\mathsf{S}} = 15000, c_{\mathsf{F}} = 35000)$
  - trt $= 2$: $e_j = (e_{\mathsf{S}} = 26, e_{\mathsf{F}} = 22)$, $c_j = (c_{\mathsf{S}} = 7000, c_{\mathsf{F}} = 13000)$
- Often add some path-specific **initial costs**
  - trt $= 1$: $c_0 = 3000$
  - trt $= 2$: $c_0 = 500$
- Assign probabilities to each **chance node** p_j
  - trt $= 1$: $p_j = (p_{\mathsf{S}} = 0.75, p_{\mathsf{F}} = 0.25)$
  - trt $= 2$: $p_j = (p_{\mathsf{S}} = 0.93, p_{\mathsf{F}} = 0.07)$

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Decision Trees - forward computation

- Calculate **total values** $v_j^\star = (e_j^\star, c_j^\star)$ for each path:
  - trt $= 1$: $e_j^\star = (e_\mathsf{S} + e_\mathsf{F})$, $c_j^\star = (c_0 + c_\mathsf{S} + c_\mathsf{F})$
  - trt $= 2$: $e_j^\star = (e_\mathsf{S} + e_\mathsf{F})$, $c_j^\star = (c_0 + c_\mathsf{S} + c_\mathsf{F})$
- Calculate **joint probabilities** $p_j^\star$ for each path
  - trt $= 1$: $p_j^\star = (p_\mathsf{S}, p_\mathsf{F})$
  - trt $= 2$: $p_j^\star = (p_\mathsf{S}, p_\mathsf{F})$
- Calculate **expected total value** $\mathsf{E}[V]$ as weighted average for each outcome and path

$$\mathsf{E}[V] = \sum_{j=1}^{m} v_j^\star p_j^\star$$

Decision Trees - forward computation

- Compute **incremental** CE quantities using **expected values**:
  - $\Delta_c = \mathsf{E}[c \mid \theta, \mathsf{trt}_2] - \mathsf{E}[c \mid \theta, \mathsf{trt}_1]$
  - $\Delta_e = \mathsf{E}[e \mid \theta, \mathsf{trt}_2] - \mathsf{E}[e \mid \theta, \mathsf{trt}_1]$
  - $\mathsf{ICER} = \frac{\Delta_c}{\Delta_e}$
  - $\mathsf{INMB} = k \times \Delta_e - \Delta_c$ (eg $k = 20000$)

Decision Trees - forward computation

- Compute **incremental** CE quantities using **expected values**:
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  - $\mathsf{ICER} = \frac{\Delta_c}{\Delta_e}$
  - $\mathsf{INMB} = k \times \Delta_e - \Delta_c$ (eg $k = 20000$)
- For instance, in our example:

	Costs	**QALYs**	**Delta_c**	**Delta_e**	**ICER**	**INMB**
Trt1	23000	30.00				
Trt2	7920	25.72	15080	4.28	3523	70520

Decision Trees - sensitivity analysis

- Two main types of **uncertainty analyses** :
  - **Stochastic**: around a *realisation* at the individual level
  - **Parameter**: around model *input parameters*

Decision Trees - sensitivity analysis

- Two main types of **uncertainty analyses** :
  - **Stochastic**: around a *realisation* at the individual level
  - **Parameter**: around model *input parameters*
- Exploring impact of uncertainty on model results, often called **sensitivity analysis**, which may be:
  - **Deterministic** (DSA): vary parameters *separately* using a *fixed set of values* (eg low/high)
  - **Probabilistic** (PSA): vary parameters *jointly* using sampling from *probability distributions*

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  - **Probabilistic** (PSA): vary parameters *jointly* using sampling from *probability distributions*
- **PSA** consists in sampling $s = 1 \ldots, S$ random inputs $\theta(s)$ from a selected distribution $p(\theta)$ to obtain samples of pairs $(\Delta_e(s), \Delta_c(s))$:
  - $\Delta_e(s) = \mathsf{E}[e \mid \theta(s), \mathsf{trt}_2] - \mathsf{E}[e \mid \theta(s), \mathsf{trt}_1]$
  - $\Delta_c(s) = \mathsf{E}[c \mid \theta(s), \mathsf{trt}_2] - \mathsf{E}[c \mid \theta(s), \mathsf{trt}_1]$

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Decision Trees - PSA

- For example, we may generate S values for c_0 for each treatment by sampling them from *Gamma distributions*, indexed by some *shape* and *scale* parameter values, chosen based on the **context** to generate reasonable outcome values:
  - $c_0(s) \mid \text{trt}_1 \sim \text{Gamma}(\text{shape} = c_0/500, \text{scale} = 500)$
  - $c_0(s) \mid \text{trt}_2 \sim \text{Gamma}(\text{shape} = c_0/670, \text{scale} = 670)$

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  - $c_0(s) \mid \text{trt}_2 \sim \text{Gamma}(\text{shape} = c_0/670, \text{scale} = 670)$
- Use similar approach for other parameters, eg **QALYs** & **costs** :
  - $c_S(s) \mid \text{trt}_j \sim \text{Gamma}(c_S/100, 100)$
  - $c_F(s) \mid \text{trt}_j \sim \text{Gamma}(c_F/200, 200)$
  - $e_S(s) \mid \text{trt}_j \sim \text{Gamma}(e_S/0.3, 0.3)$
  - $e_F(s) \mid \text{trt}_j \sim \text{Gamma}(e_F/0.6, 0.6)$

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  - $e_S(s) \mid \text{trt}_j \sim \text{Gamma}(e_S/0.3, 0.3)$
  - $e_F(s) \mid \text{trt}_j \sim \text{Gamma}(e_F/0.6, 0.6)$
- For simplicity, assume *fixed values* for **probabilities** p_j

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Decision Trees - CE results in PSA

- **PSA** gives S different estimates for each derived quantity, eg **incremental differences** $\Delta_c(s)$ and $\Delta_e(s)$

	Delta_c	Delta_e
1	13518.28	7.013
2	14836.93	7.301
3	12721.06	7.125
4	17916.61	4.165
5	13923.28	6.668
6	18499.22	-4.891

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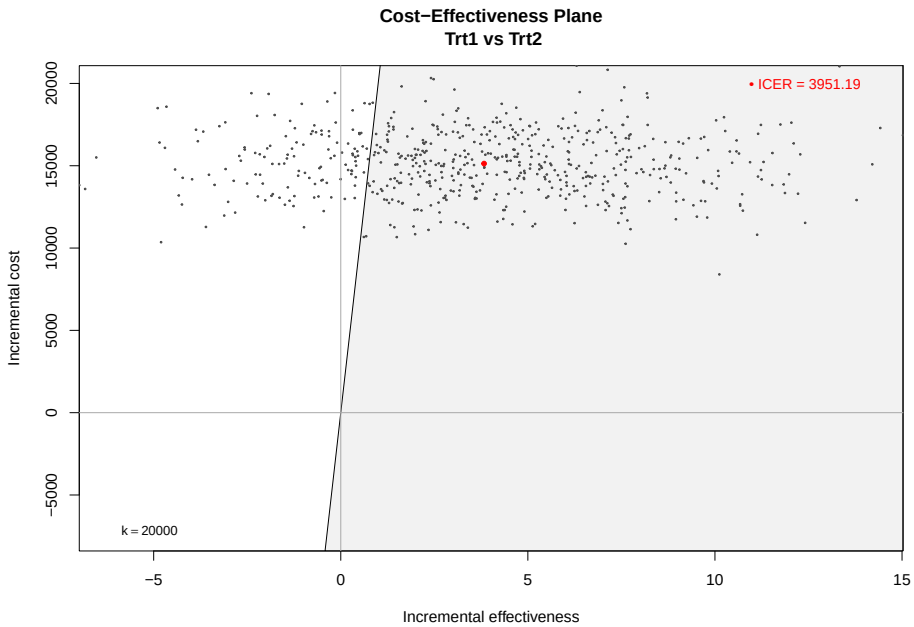
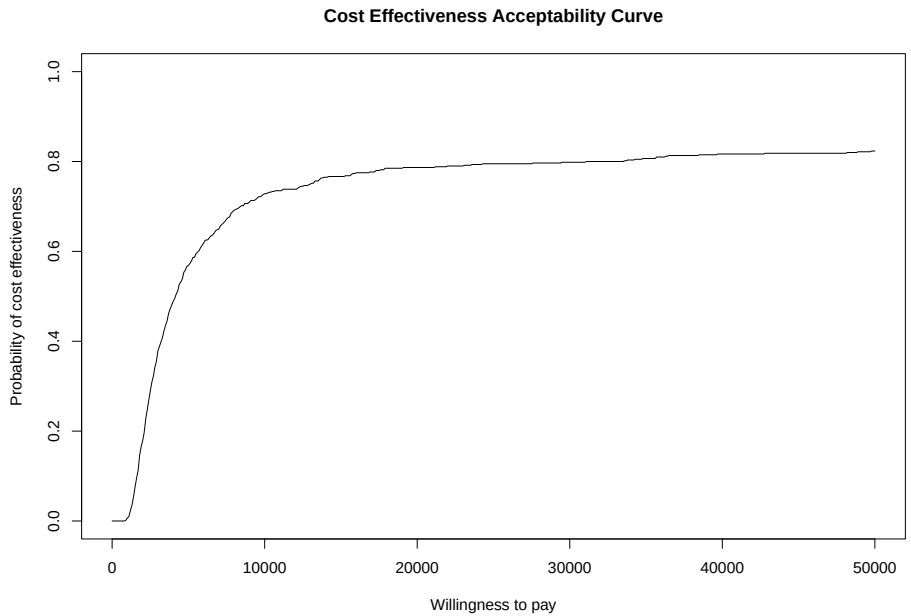
- Can summarise these by looking at average values across the S samples and use them to compute **CE measures**, eg ICER $= \frac{\mathsf{E}_s[\Delta_c(s)]}{\mathsf{E}_s[\Delta_e(s)]}$

	Costs	QALYs	Delta_c	Delta_e	ICER	INMB
Trt1	23098	29.882				
Trt2	7967	26.053	15131	3.83	3951	61460

Decision Trees - CE results in PSA

- Or use all S samples to generate **CE graphs**, eg CE plane and CEAC





Decision Trees - conclusions

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- Structure could be extended to account for these events (eg disease recurrence) **BUT**:
  - as complexity increases, modelling becomes **inefficient**
  - interpretation of the results becomes **more challenging**
- Suited for modelling **diagnostic technologies** and **screening programmes** (eg false positives, true positives, etc.)
  - **time dependency** and **long-term** disease processes or outcomes *not relevant*

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Markov Models

- Alternative to decision trees for simulating diseases/treatments with **long-term** consequences and **repeating** events
  - simulate nature of disease progression through **health states**
  - estimate expected **costs**/**benefits** associated with each state
  - states are **mutually exclusive** and **exhaustive**
  - represented through **state-transition** (S-T) diagrams

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- Alternative to decision trees for simulating diseases/treatments with **long-term** consequences and **repeating** events
  - simulate nature of disease progression through **health states**
  - estimate expected **costs**/**benefits** associated with each state
  - states are **mutually exclusive** and **exhaustive**
  - represented through **state-transition** (S-T) diagrams
- **Example**: colon cancer
  - Three **treatments**: *No trt* (None), *trt A* (A), *trt AB* (AB)
  - Four **states**: *Recurrence-free* (RF), *Recurrence* (R), *Dead-all cause* (OCD), *Dead-cancer* (CD)
  - **Transitions** allowed:

$$RF \rightarrow (R, OCD);\ R \rightarrow (OCD, CD);\ RF \rightarrow (R, OCD, CD)$$

  - model is **irreversible** (back-movement not allowed)
  - Death states are **absorbing** (capture final movement)

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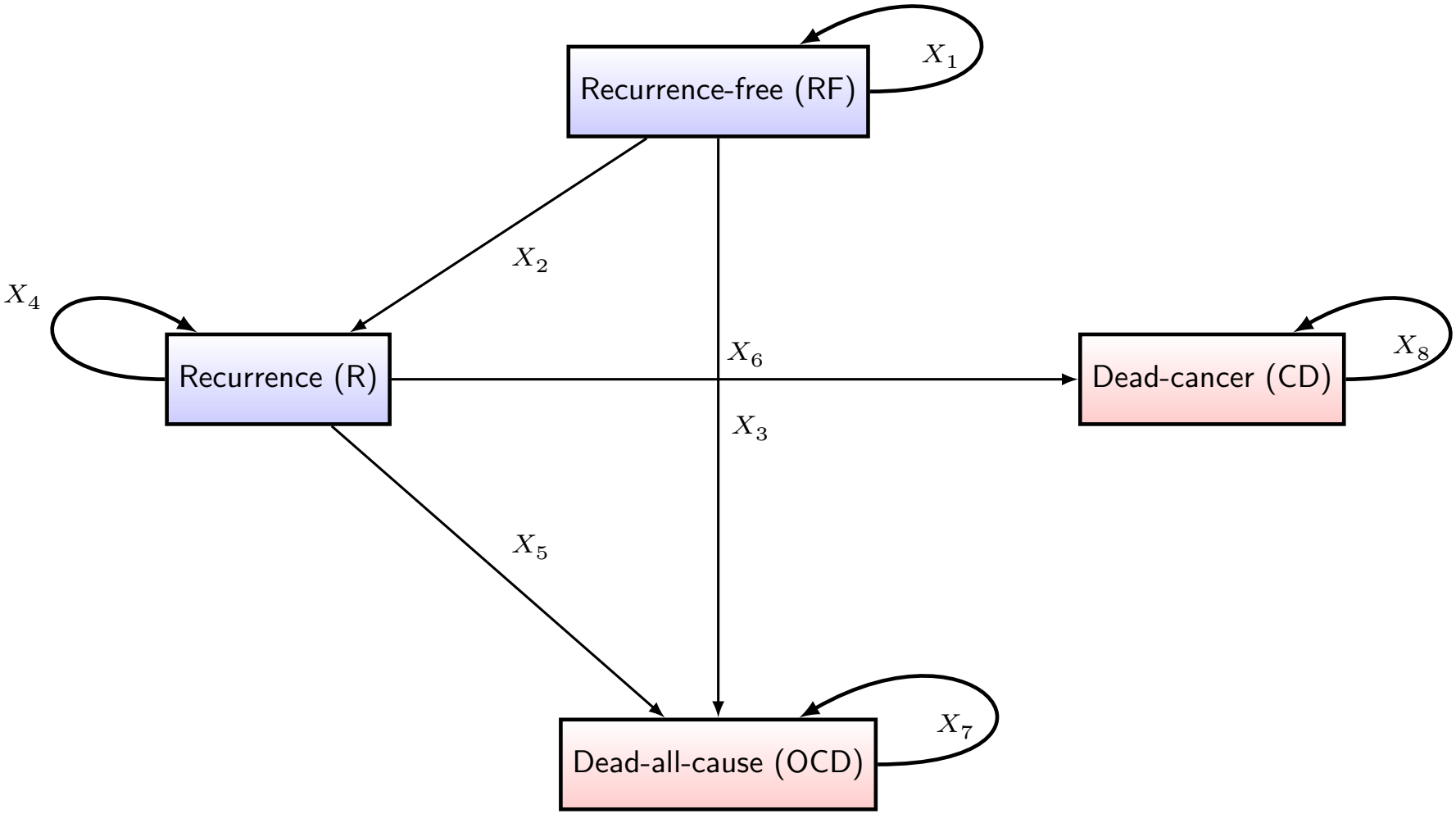
Markov Models - example

- **S-T Diagram**: *states* = squares; *transitions* = arrows



Markov Models - transition probabilities

- Need to define values of **transition probabilities**:
  - Chance of individuals to move between states alongside allowed paths
  - Organised in **transition matrices**

	RF	**R**	**OCD**	**CD**
RF	X1	X2	X3	0
R	0	X4	X5	X6
OCD	0	0	X7	0
CD	0	0	0	X8

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CD	0	0	0	X8

- Distinction made between two state-transition model **types**:
  - **discrete**: transitions at a given time point (eg monthly)
  - **continuous**: transitions at any time along an interval

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Markov Models - discrete time

- **Discrete** time points often called **cycles**:
  - Their **length** (duration) is chosen according to nature of disease/intervention
  - If short enough given the context $\rightarrow$ discretisation bias acceptable
  - balance between **short length** and **data availability** for probabilities

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- At each cycle individuals in a state may **move** to other states:
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  - Often $T =$ entire **lifetime horizon** of the individuals

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  - According to values of **transition probabilities**
  - Repeated for a number of cycles T - **time horizon** of the model
  - Often $T =$ entire **lifetime horizon** of the individuals
- Probabilities often chosen from the **literature** or estimated from **data**
  - **Problem**: May not be available for a given cycle length
  - **Solution**: Transform probabilities between different time frames

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Markov Models - converting probabilities

- A 5-month **transition probability** $p(t = 5)$ available but:
  - model has cycle length of $t = 1$ month
  - cannot simply divide **probabilities**

Markov Models - converting probabilities

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  - cannot simply divide **probabilities**
- Convert $p(t)$ into a **rate** $r(t)$ for desired t:
  - $r(t) =$ *instantaneous* measure of change over given time frame t
  - Get $r(t = 1) = -\frac{\log(1-p(t=5))}{5}$ over re-scaled time $t = 1$
  - Assume **constant rate over time** for two events

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  - Assume **constant rate over time** for two events
- Convert $r(t)$ back to a **probability** $p(t)$
  - $p(t)$ transformed probability at given time point t
  - Get $p(t = 1) = 1 - e^{-r(t=1)\times 1}$ at re-scaled time $t = 1$

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Markov Models - converting probabilities

- Often published data in the form of **odds**:
  - odds $= \frac{p}{(1-p)}$
  - ratio of event **probability** p over its complement

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  - OR $= \frac{p_1/(1-p_1)}{p_2/(1-p_2)}$
  - ratio of **odds** for two event probabilities (eg success probability of two competing treatments)

Markov Models - converting probabilities

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  - ratio of **odds** for two event probabilities (eg success probability of two competing treatments)
- Can convert *log(odds)* to p scale using the **inverse logistic** function:
  - $p = \frac{e^{\log(\text{odds})}}{1+e^{\log(\text{odds})}}$
- Can convert p to *log(odds)* scale using the **logistic** function:
  - $\log(\text{odds}) = \log(p/(1-p))$

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Markov Models - Markov assumption

- **Markov Assumption**: movement from current state to a future one, **conditional** on both *past* and *present* states, **depends only** on the *current* state and not on the *past* states

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- Both model types can be implemented either at:
  - **Cohort level**: simulate a closed *homogeneous* group of individuals
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- Both model types can be implemented either at:
  - **Cohort level**: simulate a closed *homogeneous* group of individuals
  - **Individual level**: simulate single, possibly *heterogeneous*, individuals
- Here, we focus on two types of **cohort** Markov models:
  - **time-homogeneous**: transition probabilities *constant* over cycles
  - **time-inhomogeneous**: transition probabilities *may change* over cycles

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Markov Models - Time-Homogeneous

- Consider our colon cancer example:
  - **Transition matrix** has dimensions 4×4 (four states)
  - Rows must sum up to 1 (*mutually exclusive and exhaustive*)
  - **Zeros** indicate movements between states not allowed
- **Transition matrix**, eg for the "no treatment" group (None):

	Recurrence-free	**Recurrence**	**Dead(all cause)**	**Dead(cancer)**
Recurrence-free	0.817	0.063	0.12	0.00
Recurrence	0.000	0.450	0.12	0.43
Dead(all cause)	0.000	0.000	1.00	0.00
Dead(cancer)	0.000	0.000	0.00	1.00

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Markov Models - Time-Homogeneous

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  - Everyone starts in RF state and no one in the other states
  - π_1 shows that 100% of the cohort is in RF and 0% in all the others

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- The **Markov trace** π_t gives information about how the cohort is *proportionally distributed* across the states at each cycle t
- In our example, at $t = 1$:
  - Everyone starts in RF state and no one in the other states
  - π_1 shows that 100% of the cohort is in RF and 0% in all the others
- At $t = 2, \ldots, T$, individuals transition to other states:
  - π_{t+1} computed using **transition matrix** P: $\pi_{t+1} = \pi_t P$
  - obtain distribution of individuals transitioning from their *current* state to *other* states at $t + 1$
  - check model behaviour compared to **expected clinical context**

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Markov Models - Time-Homogeneous

- The **Markov trace** π_t gives information about how the cohort is proportionally distributed across the states at each cycle t
- For instance, we can look at π_t at $t = \{1, 2, 3, 4, 5\}$ (eg for None):

	Recurrence-free	Recurrence	Dead(all cause)	Dead(cancer)
1	1.000	0.000	0.000	0.000
2	0.817	0.063	0.120	0.000
3	0.667	0.080	0.226	0.027
4	0.545	0.078	0.315	0.061
5	0.446	0.069	0.390	0.095

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Markov Models - costs

- Treatment-specific **costs** often simulated by associating them with each **state** rather than **transitions**

Markov Models - costs

- Treatment-specific **costs** often simulated by associating them with each **state** rather than **transitions**
- In our case, cost of a *recurrence* (eg 35000) not straightforward to incorporate:
  - associate cost of a recurrence to **Recurrence-Free** state $c_{RF} = 35000$
  - weight it by the **probability of a recurrence** $c^{\star}_{RF} = 35000 \times p_{RF-R}$
  - to calculate the **average cost** of recurrence events

	Recurrence-free	Recurrence	Dead(all cause)	Dead(cancer)
None	2205	0	0	0
A	2380	0	0	0
AB	1680	0	0	0

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Markov Models - utilities

- State-specific **utilities** u_s multiplied by the **cycle length**
  - to get associated **QALYs** accrued from spending one cycle in each state
  - when **cycle length** is one year, cycle **utilities** and **QALYs** coincide
  - often assumed to be the same across treatments

Recurrence-free	0.8
Recurrence	0.6
Dead(all cause)	0.0
Dead(cancer)	0.0

Markov Models - costs and utility losses

- If applicable, the impact on **costs** and **utilities** of relevant **events** (eg due to *toxicity*) can be taken into account based on:
  - toxicity **costs** $c_{\text{tox}} = 2000$
  - toxicity **disutilities** $u_{\text{tox}} = -0.1$
  - toxicity **probabilities** $p_{\text{tox,trt}}$
- These can be added to the totals to compute treatment-specific average **costs** and **disutilities**:
  - $c_{\text{trt}} = c_{0,\text{trt}} + c_{\text{tox}} \times p_{\text{tox,trt}}$
  - $u_{\text{trt}} = u_{\text{tox}} \times p_{\text{tox,trt}}$

	None	A	AB
Costs	0	5400.00	10800.00
QALYs	0	-0.02	-0.04

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Markov Models - discounting

- **Time horizon**, ie number of cycles T, goes beyond 1 year:
  - need to discount total **costs** and **QALYs** at annual **discount rate** d
  - compute **discount factor** at cycle t: $d(t) = \frac{1}{(1+d)^t}$
  - in the Netherlands: $d^c = 3\%$ and $d^e = 1.5\%$

Markov Models - discounting

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  - compute **discount factor** at cycle t: $d(t) = \frac{1}{(1+d)^t}$
  - in the Netherlands: $d^c = 3\%$ and $d^e = 1.5\%$
- First, multiply cycle-specific proportions in **Markov trace** π_t to **state-specific outcomes** (c_{RF}, u_s) and sum them to obtain total **cycle-specific values** $(c(t), u(t))$ for each treatment

	Cycle 0	Cycle 1	Cycle 2	Cycle 3	Cycle 4
None	2205	1801.485	1471.813	1202.471	982.419
A	2380	1932.560	1569.239	1274.222	1034.668
AB	1680	1397.760	1162.936	967.563	805.012

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Markov Models - compute total costs and QALYs

- Then:
  - multiply **cycle-specific outcomes** $(c(t), u(t))$ to **discount** factors $d(t)$ and sum them across cycles
  - add **treatment-specific outcomes** $(c_{\text{trt}}, u_{\text{trt}})$ to obtain **total values** for each treatment $(c_{\text{tot}}, u_{\text{tot}})$

	None	A	AB
Costs	10352.016	16317.356	19284.65
QALYs	4.378	4.304	4.72

- Finally, get **incremental** CE quantities for trt $= (A, AB)$ vs None:
  - Incremental costs: $\Delta_c = c_{\text{tot,trt}} - c_{\text{tot,None}}$
  - Incremental Effects: $\Delta_e = u_{\text{tot,trt}} - u_{\text{tot,None}}$
  - Incremental CE Ratio: ICER $= \frac{\Delta_c}{\Delta_e}$
  - Incremental NMB: INMB $= \Delta_e \times k - \Delta_c$ (eg $k = 10000$)

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Markov Models - compute total costs and QALYs

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- Finally, get **incremental CE quantities** for trt $= (A, AB)$ vs None:

	Delta_c	Delta_e	ICER	INMB
None				
A	5965	-0.075	-80010	-6711
AB	8933	0.342	26140	-5515

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Markov Models - Time-Inhomogeneous

- In our case, **transition probabilities** may be **time-dependent**, for example, because:
  - Recurrence probabilities depend on *time since treatment initiation*
  - All-cause death probabilities depend on *age*
  - Cancer-death probabilities depend on *time since recurrence*
- Due to **cohort** structure of the model, **time-dependency**:
  - can be recorded in terms of **time-in-model** - eg, since treatment initiation or age
  - cannot be recorded in terms of **time-in-state** - eg, since recurrence
- Need to define **transition matrix** where probabilities are defined for each treatment and cycle:
  - **time-dependency function** to say how probabilities change over time
  - if reasonable, cycle-specific probabilities can be filled-in more easily

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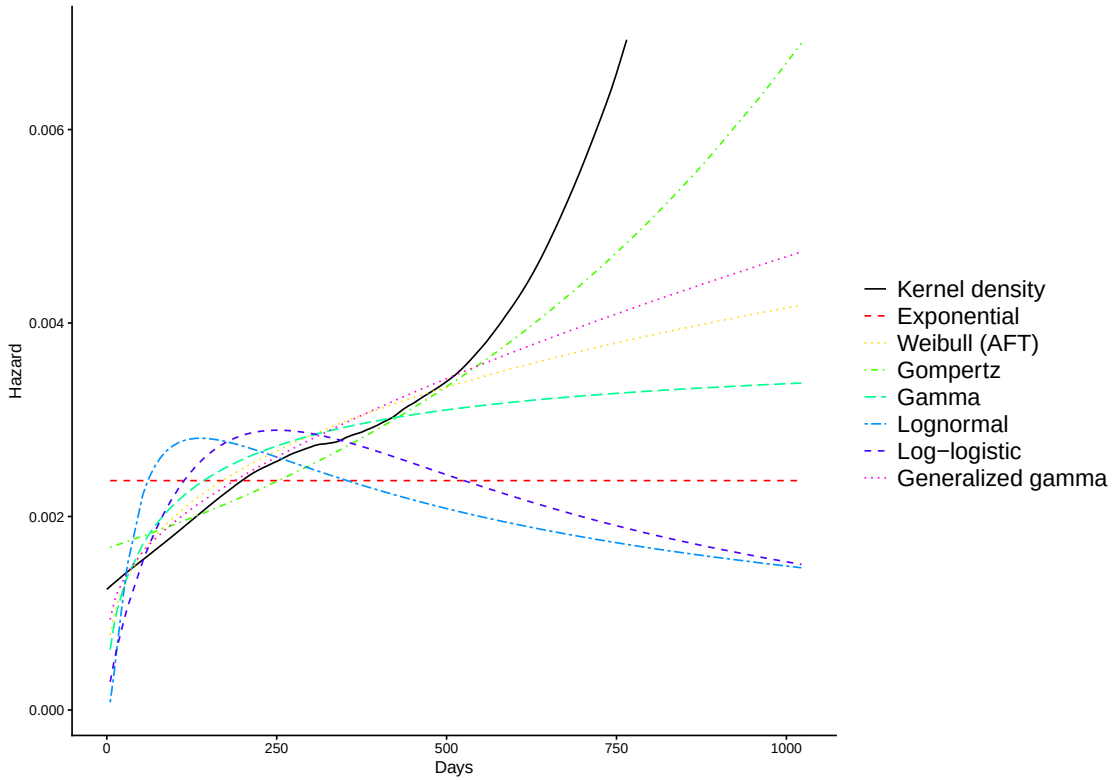
Markov Models - time-dependent probabilities

- Probabilities for **death states** estimated via **survival analysis**:
  - Alternative **survival functions** used to express *time-mortality* relation
  - Fitted to relevant data (eg life tables) and compared using **standard measures** (eg *Akaike Information Criterion* - AIC)
  - **Cumulative hazard function** gives probabilities $RF \rightarrow OCD$



Markov Models - time-dependent probabilities

- Probabilities for **non-death states** can be derived similarly using **probabilistic functions**
  - eg, *Log-logistic function* used to estimate probability $RF \rightarrow R$
  - estimated parameter values used to generate probabilities at each cycle in the model

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- Probability $R \rightarrow CD$ **time-independent** since model cannot capture **time-in-state**:
  - eg, *Exponential* function parameter estimated from *log rates* and *rate ratios* of treatments

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  - estimated parameter values used to generate probabilities at each cycle in the model
- Probability $R \rightarrow CD$ **time-independent** since model cannot capture **time-in-state**:
  - eg, *Exponential* function parameter estimated from *log rates* and *rate ratios* of treatments
- Fill-in probabilities in **transition matrices** at each cycle for each treatment

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Markov Models - time-dependent probabilities

- For instance, for "None" treatment at cycle 1

	Recurrence-free	Recurrence	Dead(all cause)	Dead(cancer)
Recurrence-free	0.721	0.271	0.008	0.000
Recurrence	0.000	0.561	0.008	0.431
Dead(all cause)	0.000	0.000	1.000	0.000
Dead(cancer)	0.000	0.000	0.000	1.000

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Markov Models - time-dependent probabilities

- For instance, for "None" treatment at cycle 2

	Recurrence-free	Recurrence	Dead(all cause)	Dead(cancer)
Recurrence-free	0.704	0.286	0.009	0.000
Recurrence	0.000	0.560	0.009	0.431
Dead(all cause)	0.000	0.000	1.000	0.000
Dead(cancer)	0.000	0.000	0.000	1.000

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Markov Models - time-dependent probabilities

- For instance, for "None" treatment at cycle 3

	Recurrence-free	**Recurrence**	**Dead(all cause)**	**Dead(cancer)**
Recurrence-free	0.753	0.237	0.01	0.000
Recurrence	0.000	0.559	0.01	0.431
Dead(all cause)	0.000	0.000	1.00	0.000
Dead(cancer)	0.000	0.000	0.00	1.000

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Markov Models - time-dependent Markov trace

- Next, calculate **Markov trace** using *cycle-dependent* **transition probabilities** for each treatment
- For instance, for "None" treatment at first few cycles

	Recurrence-free	Recurrence	Dead(all cause)	Dead(cancer)
Cycle 0	1.000	0.000	0.000	0.000
Cycle 1	0.721	0.271	0.008	0.000
Cycle 2	0.508	0.358	0.018	0.117
Cycle 3	0.382	0.320	0.026	0.271
Cycle 4	0.303	0.254	0.034	0.409
Cycle 5	0.250	0.191	0.041	0.518

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Markov Models - costs and utilities

- Computation of treatment-specific **costs** and **utilities** is mostly similar to that of the homogeneous model

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- **Costs**:
  - **state costs** $c_s(t)$ time-dependent as from **transition matrices**
  - **cycle costs** $c(t)$ computed as product between **Markov trace** π_t and $c_s(t)$, which are then summed across states at each cycle t
  - **total costs** computed as product between $c(t)$ and **discount** factors $d^c(t)$, summed across cycles, and then added to **treatment costs** (c_{trt})

Markov Models - costs and utilities

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  - **total costs** computed as product between $c(t)$ and **discount** factors $d^c(t)$, summed across cycles, and then added to **treatment costs** (c_{trt})
- **Utilities**:
  - **state utilities** u_s time-independent
  - **cycle utilities** $u(t)$ computed as product between π_t and u_s at t
  - **total utilities** computed as product between $u(t)$ and **discount** factors $d^e(t)$, summed across cycles, and added to **treatment disutilties** (u_{trt})

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Markov Models - CE results

- Total outcome values per treatment and **incremental** CE results can then be computed as per usual

	Costs	QALYs	Delta_c	Delta_e	ICER	NMB	INMB
None	32311	4.770				15388	
A	38135	4.568	5824	-0.202	-28846	7544	-7844
AB	38929	6.332	6619	1.563	4236	24395	9007

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Markov Models - implementing PSA

- Impact of **parameter uncertainty** must be assessed via **PSA**:
  - introduce *probabilistic modelling* of parameters
  - generate a "sufficient" number of samples S from distributions
  - run the model at each parameter sampled values
  - obtain **distributions** for CE quantities (eg INMB)
- **Key changes**:
  - include an extra dimension to all model elements (eg **transition matrices**) for the S parameter samples
  - choose appropriate distributions for most/all model parameters (eg *Gamma* for costs)
  - if possible, account for the **correlation** between key parameters via **joint distributions**

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Markov Models - choosing parameter distributions

- **Transition probabilities** $RF \rightarrow R$ specified using *log-logistic cure model*, indexed by three parameters: *log-odds*, *shape*, *scale*

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Markov Models - choosing parameter distributions

- **Transition probabilities** $RF \rightarrow R$ specified using *log-logistic cure model*, indexed by three parameters: *log-odds, shape, scale*
- Account for **correlation** via *joint normality* for each treatment:
  - set mean values equal to point values in base-case analysis
  - fill-in covariance matrix values based on literature/expert opinion

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Markov Models - choosing parameter distributions

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- Account for **correlation** via *joint normality* for each treatment:
  - set mean values equal to point values in base-case analysis
  - fill-in covariance matrix values based on literature/expert opinion
- For example, for the no treatment option ("None"):

$$\begin{pmatrix} \text{log-odds} \\ \text{shape} \\ \text{scale} \end{pmatrix} \sim \text{Normal}\left[\begin{pmatrix} -0.4398 \\ 0.4597 \\ 0.1379 \end{pmatrix}, \begin{pmatrix} 0.0185 & 0.0035 & -0.0037 \\ 0.0035 & 0.0063 & -0.0026 \\ -0.0037 & -0.0026 & 0.0089 \end{pmatrix}\right]$$

Markov Models - choosing parameter distributions

- **Transition probabilities** $(RF, R) \rightarrow OCD$ specified using *Gompertz* hazard function, indexed by two parameters: *shape*, *rate*

Markov Models - choosing parameter distributions

- **Transition probabilities** $(RF, R) \rightarrow OCD$ specified using *Gompertz* hazard function, indexed by two parameters: *shape*, *rate*
- In theory, could also jointly model these parameters as in $RF \rightarrow R$, but it may be *reasonable* to simplify the model:
  - if parameter estimates obtained from distributions fitted to **population-level** data (eg life tables)
  - assume values close to *true* population parameters

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  - if parameter estimates obtained from distributions fitted to **population-level** data (eg life tables)
  - assume values close to *true* population parameters
- Keep **single point** values for these parameters (same across treatments):

$$\text{shape} = 0.0885$$
$$\text{rate} = 0.0081$$

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Markov Models - choosing parameter distributions

- **Transition probabilities** $R \rightarrow CD$ specified with a different *Exponential* distribution for each treatment, indexed by the following parameters: *log rate* (None), *log rate ratios* (A, AB)

Markov Models - choosing parameter distributions

- **Transition probabilities** $R \rightarrow CD$ specified with a different *Exponential* distribution for each treatment, indexed by the following parameters: *log rate* (None), *log rate ratios* (A, AB)
- Account for **correlation** via *joint normality* among treatments:
  - set mean values equal to point values in base-case analysis
  - fill-in covariance matrix values based on literature/expert opinion

$$\begin{pmatrix} \text{log rate}_{\text{None}} \\ \text{log rate ratio}_{\text{A}} \\ \text{log rate ratio}_{\text{AB}} \end{pmatrix} \sim \text{Normal} \left[\begin{pmatrix} -0.5734 \\ 0.0548 \\ 0.0548 \end{pmatrix}, \begin{pmatrix} 0.0065 & -0.0065 & -0.0065 \\ -0.0065 & 0.0131 & 0.0065 \\ -0.0065 & 0.0065 & 0.0157 \end{pmatrix} \right]$$

Markov Models - transition matrices in PSA

- Sample S values from each distribution for each parameter:
  - Use sampled values to generate corresponding **transition probabilities**
  - Fill-in values in the **transition matrices**
  - Ensure that values sum from a given state to others (for given treatment, cycle and sample) is one

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Markov Models - transition matrices in PSA

- Sample S values from each distribution for each parameter:
  - Use sampled values to generate corresponding **transition probabilities**
  - Fill-in values in the **transition matrices**
  - Ensure that values sum from a given state to others (for given treatment, cycle and sample) is one
- For instance, we can look at the first 5 samples (columns) at the first 5 cycles (rows) related to the **transition probabilities** $RF - R$ (eg for None):

Cycle 0	0.272	0.244	0.268	0.256	0.244
Cycle 1	0.265	0.279	0.288	0.306	0.296
Cycle 2	0.217	0.238	0.239	0.259	0.251
Cycle 3	0.179	0.200	0.198	0.216	0.209
Cycle 4	0.151	0.170	0.167	0.183	0.177

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Markov Models - Markov trace in PSA

- Use **transition matrices** to construct *probabilistic* version of **Markov trace** $\pi_t(s)$:
  - Computed as before for each treatment, cycle and state, but
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  - Computed as before for each treatment, cycle and state, but
  - with an extra dimension to store S samples
- For instance, we can look at the first 5 samples (columns) at the first 5 cycles (rows) related to the **Markov trace** values for RF (None):

Cycle 0	0.000	0.000	0.000	0.000	0.000
Cycle 1	0.265	0.279	0.288	0.306	0.296
Cycle 2	0.417	0.442	0.450	0.478	0.464
Cycle 3	0.508	0.540	0.545	0.575	0.561
Cycle 4	0.565	0.599	0.601	0.632	0.619

Markov Models - costs and utilities in PSA

- Generate **state costs** $c_s(t,s) = (c_{RF}(t,s), c_R, c_{OCD}, c_{CD})$ as before:
  - $c_{RF}(t,s)$ time/sample-dependent as product between:
  - cycle/sample-specific recurrence probability
  - assumed recurrence cost (eg 40000)
  - $(c_R, c_{OCD}, c_{CD}) = 0$

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- Generate **state utilities** $u_s(s) = (u_{RF}(s), u_R(s), u_{OCD}, u_{CD})$ as before:
  - $(u_{RF}(s), u_R(s)) \overset{\text{iid}}{\sim} \text{Normal}(\mu, \sigma)$
  - time-independent but sampled from independent Normals with assumed mean μ and sd σ
  - $(u_{OCD}, u_{CD}) = 0$

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Markov Models - costs and utilities in PSA

- Generate **treatment costs** $c_{\text{trt}}(s)$ related to specific events (eg toxicity) as before:
  - $c_{\text{trt}}(s) = c_{0,\text{trt}} + c_{\text{tox}}(s) \times p_{\text{tox,trt}}(s)$
  - assume fixed point cost value for each treatment
  - sample toxicity cost from independent Normals
  - sample toxicity probs from independent Normals
- Generate **treatment disutilities** $u_{\text{trt}}(s)$ related to specific events (eg toxicity) as before:
  - $u_{\text{trt}}(s) = u_{\text{tox}}(s) \times p_{\text{tox,trt}}(s)$
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Markov Models - costs and utilities in PSA

- Compute treatment-specific **cycle costs** $c(t, s)$ and **cycle utilities** $u(t, s)$ as before:
  - product between **Markov trace** $\pi_t(s)$ and **state costs** $c_s(t, s)$ at each cycle and sample, summed across states
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  - product between **Markov trace** $\pi_t(s)$ and **state utilities** $u_s(s)$ at each cycle and sample, summed across states
- Compute treatment-specific **total costs** and **total utilities** as before:
  - product between $c(t, s)$ and **discount** factors $d^c(t)$, summed across cycles, then added to **treatment costs** $(c_{\text{trt}}(s))$
  - product between $u(t, s)$ and **discount** factors $d^e(t)$, summed across cycles, then added to **treatment utilities** $(u_{\text{trt}}(s))$

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Markov Models - CE results in PSA

- Total outcome values now available for S samples:

	costs-None	costs-A	costs-AB	qalys-None	qalys-A	qalys-AB
1	33881.48	39233.49	40961.41	10.515	10.431	10.570
2	33097.79	40576.43	41020.00	10.360	10.327	10.732
3	33859.21	37967.93	40861.53	10.729	11.156	11.315
4	33456.52	39492.29	39621.68	11.159	11.035	11.814
5	33038.56	38530.71	39628.64	9.364	9.382	9.806

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- Summarise **CE results**, for example by looking at *average values*

	Costs	QALYs	Delta_c	Delta_e	ICER	NMB	INMB
None	33926	10.375				69827	
A	39274	10.253	5397	-0.141	-38221	63259	-6809
AB	39446	11.000	5470	0.644	8497	70553	968

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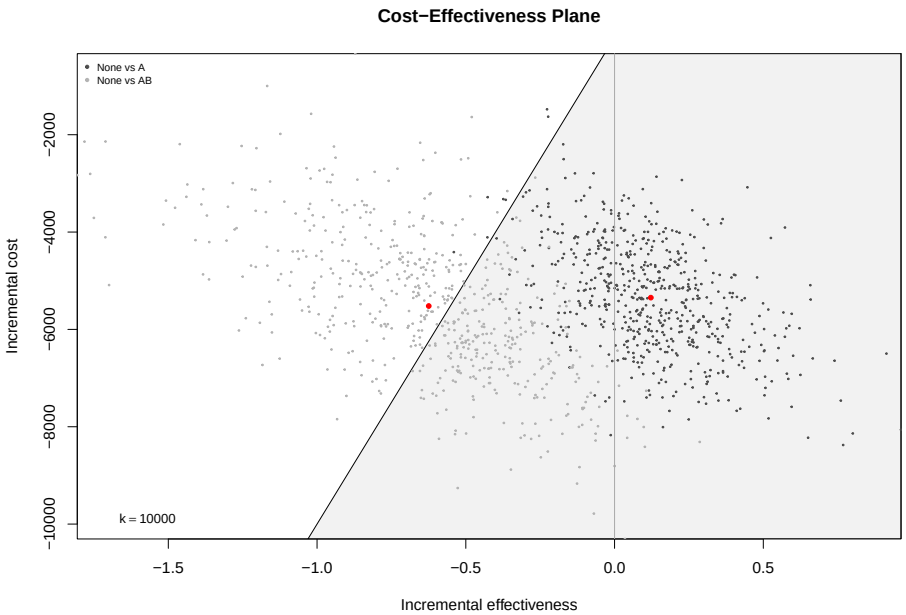
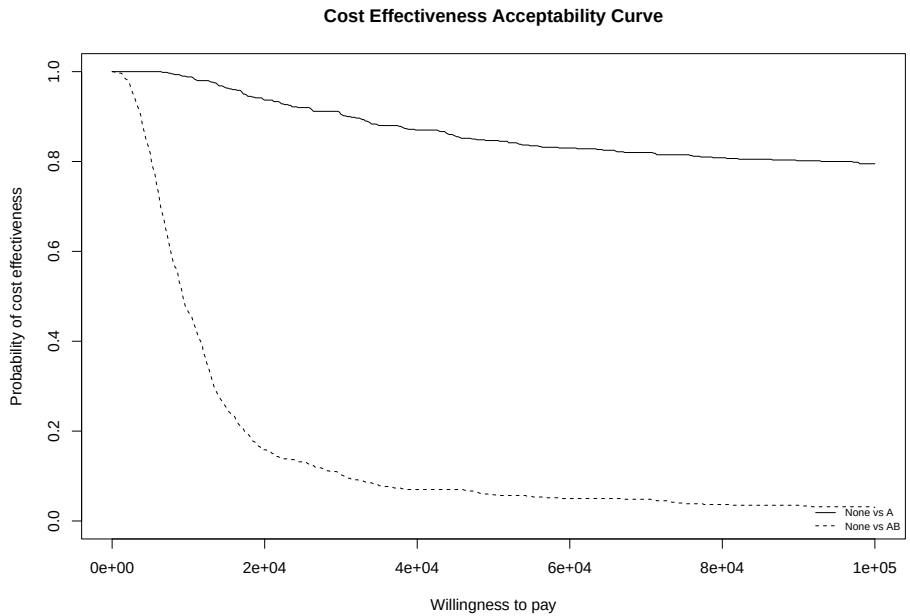
Markov Models - CE results in PSA

- Use S samples to generate standard **PSA** CE output





Markov Models - conclusions

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- **Network Meta-Analysis** (NMA) can be used to combine evidence from *multiple sources* to derive the estimate for the parameters
- Not considered **DSA** or **structural uncertainty**:
  - changing values of parameter **one at a time** across a pre-defined set of values instead of distributions
  - changing number/type of **allowed transitions** or **distributions**

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Network Meta-Analysis

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- **Network Meta-Analysis** (NMA) is primary method for **indirect** treatment comparison
  - allows to compare treatment assessed in separate trials wrt others
  - different NMA approaches exist depending on the characteristics of the **available network**
- For instance, assume interest is in treatment effect on **binary outcome** (eg pain prevention) between two drugs (A vs B) for which:
  - No *head-to-head* comparison for A vs B is available, but
  - *Odds ratios* available for A and B wrt drug C, ie OR_{AC} and OR_{BC}
  - use **direct** evidence (A vs C & B vs C) to **indirectly** compare A vs B

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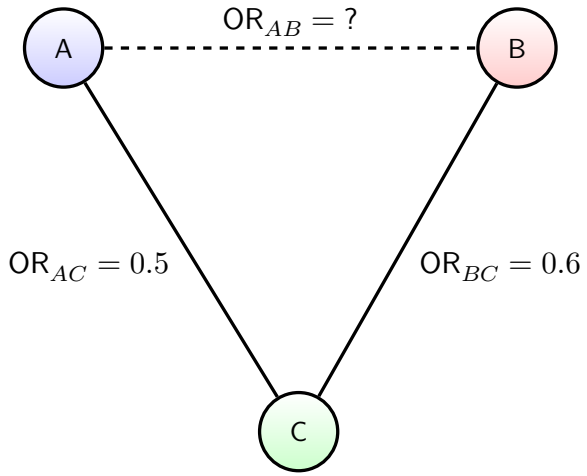
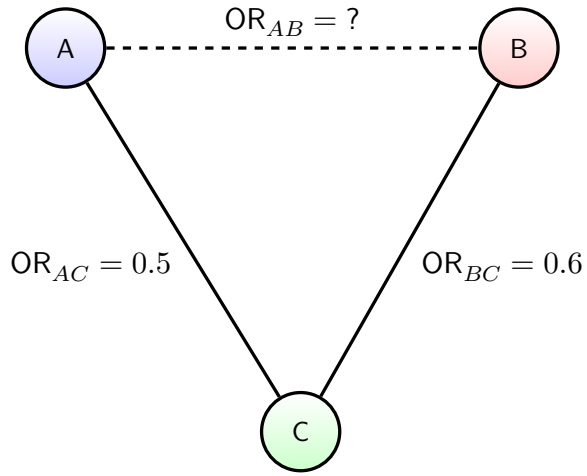
Network Meta-Analysis - example



Network Meta-Analysis - example



- An historical approach to compute OR_{AB} in this network is the **Bucher method**:
  - $OR_{AB} = \frac{OR_{AC}}{OR_{BC}} = \frac{0.5}{0.6} = 0.83$
  - on **log-odds** scale (*linear scale*): $\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$
  - where: $SE(\log(OR_{AB})) = \sqrt{SE(\log(OR_{AC}))^2 + SE(\log(OR_{BC}))^2}$

Network Meta-Analysis - example

- Suppose **evidence** about a new drug D is added to the network:
  - which is compared to B in a new trial, eg $\text{OR}_{\text{BD}} = 0.9$
  - but interest is in the comparison to A, ie $\text{OR}_{\text{AD}} = ?$
- In this case, we can apply **Bucher method** in steps:
  1. Derive OR_{AB} using **direct** evidence from the comparison between A vs C and B vs C
  2. use OR_{AB} to obtain OR_{AD} from the **indirect** evidence for A vs B and the **direct** evidence for B vs D
- NMA generalises **Bucher method** to combine **direct** and **indirect** evidence on **multiple** treatment comparisons:
  - each obtained from one or multiple sources
  - estimate uncertainty under a **consistency assumption**

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Network Meta-Analysis - methods

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- Focus on **binary outcomes** r_{ik} for treatment k in study i:
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  - $p_{ik} =$ probability of the event on treatment k in study i
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- To ensure **consistency assumption** can hold, need to convert the probability to a transformed scaled using *logistic* function
  - $\text{logit}(p_{ik}) = \log\left(\frac{p_{ik}}{1-p_{ik}}\right)$
  - scale of the *log odds* and *log odds ratios*

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  - scale of the *log odds* and *log odds ratios*
- Then model the transformed probabilities using a **linear predictor** :
  - $\text{logit}(p_{ik}) = \mu_i + \delta_{ibk}$
  - δ_{ibk} = *log odds ratios* for treatment k vs b (baseline) in trial i

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Network Meta-Analysis - methods

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  - **fixed effects**: $\delta_{ibk} = d_{i1k} - d_{i1b}$ - same across studies
  - **random effects**: $\delta_{ibk} \sim \text{Normal}(d_{i1k} - d_{i1b}, \sigma^2)$ - come from a Normal distribution with **heterogeneity** variance σ^2

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- **Heterogeneity** refers to variation in treatment effects across studies
  - choice between **fixed** and **random** effects based on assessment of extent of heterogeneity (eg, baseline characteristics, outcome definitions, time points, etc.)
  - high $\sigma^2 \rightarrow$ **random effects**(eg, if σ is considerably larger than *log odds ratios*)

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Network Meta-Analysis - estimation & assessment

- NMA conducted under either a **frequentist** or **Bayesian** approach

Network Meta-Analysis - estimation & assessment

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- **Bayesian**:
  - parameters (eg σ) **random variables** with distributions called *priors*
  - represent beliefs about parameter values **before** observing the data
  - can be *informative* or *vague* based on whether they convey or not **external information** into the model
  - priors combined with data to obtain *posterior* distributions
  - **relative model fit** assessed via **Deviance Information Criterion** (DIC)
- **frequentist**:
  - **model fit** assessed from an estimate of the total σ in network Q_{tot}
  - generalised Cochran's Q used in *pairwise* meta-analyses to test the between study heterogeneity
  - produce I^2 statistic applicable to NMA (between $[0, 100]\%$ with higher values indicating a higher amount of heterogeneity)

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Network Meta-Analysis - Meta-Regression

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- Assume pairwise meta-analysis of three trials, where:
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- If age is a **treatment effect-modifier**, ie trial-specific treatment effects are related to age, can use meta-regression model $\delta_{i12} = d_{12} + x_i\beta$, where β has to be estimated
- Extend framework to NMA (binary outcomes): $\text{logit}(p_{ik}) = \mu_i + \delta_{ibk} + x_{ik}\beta_{ibk}$
  - x_{ik} = trial/arm-specific covariate value
  - β_{ibk} = trial-specific treatment-covariate **interaction**
  - where $\beta_{ibk} = \beta_{ik} - \beta_{ib}$

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Network Meta-Analysis - case study

- Apply methods to NMA of irrigation and intracavity lavage techniques to prevent *Surgical Site Infections* (SSIs) - Thom et al. 2012

study	trt	r	n	contamination_level	surgery_type
Al-shehri 1994	nonantibacterial	7	134	1	0
Al-shehri 1994	antibiotic	1	120	1	0
Baker 1994	nonantibacterial	17	150	0	0
Baker 1994	antibiotic	17	150	0	0
Carl 2000	nonantibacterial	1	20	0	0
Carl 2000	antibiotic	1	20	0	0

- Data form 39 studies on:
  - treatment (`trt`), number of SSIs (`r`) and patients (`n`), and two binary covariates (`contamination_level`, `surgery_type`)

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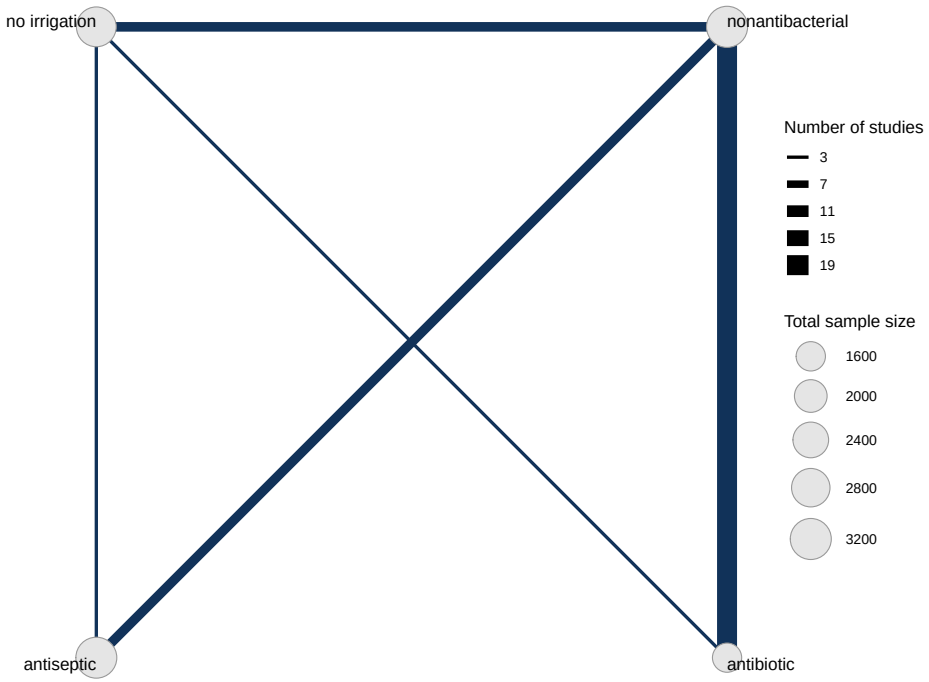
Network Meta-Analysis - Bayesian NMA

- Use `multinma` `R` package to fit model using Bayesian software `Stan` (Carpenter et al. 2017)

Network Meta-Analysis - Bayesian NMA

- Use `multinma` `R` package to fit model using Bayesian software `Stan` (Carpenter et al. 2017)
- First, check the **network**:
  - nodes → treatments and patients (size)
  - edges → comparisons and studies (thickness)



Network Meta-Analysis - Bayesian NMA

- Fit **fixed** or **random** effects models

```
> icl_nma_fe <- nma(icl_network, trt_effects = "fixed",
+     prior_intercept = normal(scale=100), #log odds
+     prior_trt = normal(scale = 100)) #log OR
>
> icl_nma_re <- nma(icl_network, trt_effects = "random",
+     prior_intercept = normal(scale=100),
+     prior_trt = normal(scale = 100),
+     prior_het = half_normal(scale = 2.5)) #sigma
```

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Network Meta-Analysis - Bayesian NMA

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```

- Compare **model fit** using **DIC**:
  - DIC(FE) = 182.2
  - DIC(RE) = 147.4

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Network Meta-Analysis - Bayesian NMA

- Look at **estimates** of the chosen model for the **relative effects** vs *reference* (nonantibacterial irrigation)

parameter	**mean**	**2.5%**	**97.5%**
d[antibiotic]	0.447	0.276	0.667
d[antiseptic]	0.586	0.324	0.941
d[no irrigation]	0.994	0.546	1.665

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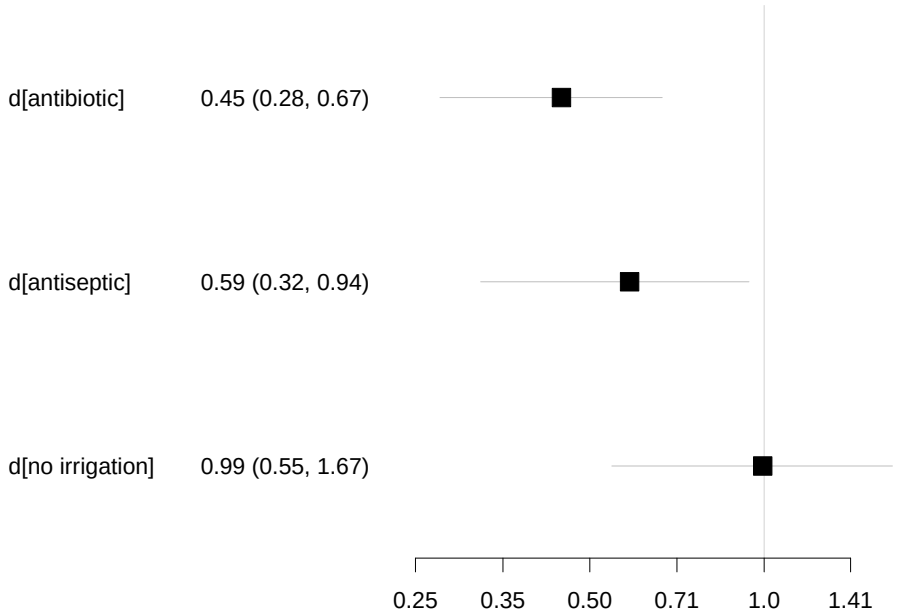
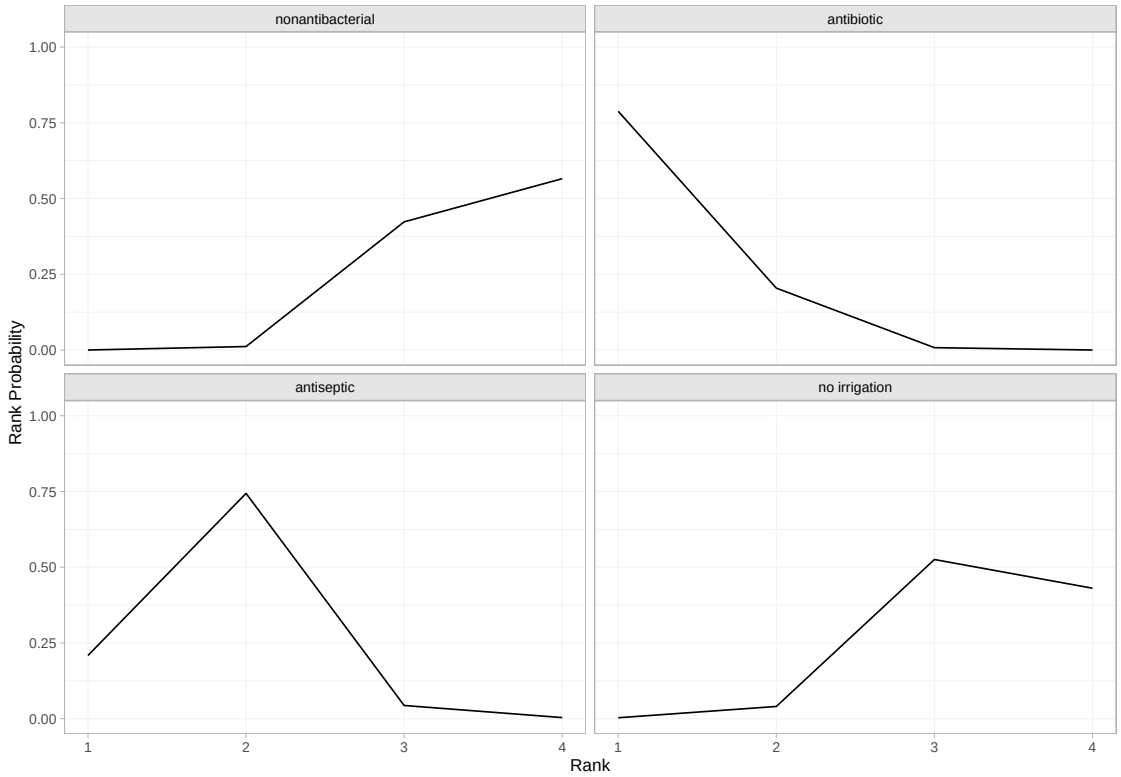
- Create **forest plots** using these estimates



Network Meta-Analysis - Bayesian NMA

- Check overall performance in terms of **treatment rankings**
  - summarise results in terms of *posterior* mean (CIs) rank
  - compute **posterior probabilities** of occupying a rank
  - plot them using a **rankogram**



Network Meta-Analysis - Bayesian NMR

- Use NMR to check if `contamination_level` (0=clean, 1=contaminated) is a **treatment effect-modifier**

```
> icl_re_nmr <- nma(icl_network, trt_effects = "random",
+     regression = ~.trt:contamination_level, #inter
+     class_interactions = "common", #common inter
+     prior_intercept = normal(scale=100),
+     prior_trt = normal(scale = 100),
+     prior_het = half_normal(scale = 2.5),
+     prior_reg = normal(scale = 100), #log OR inter
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```

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```

- Compare **model fit** using **DIC**:
  - DIC(RE) = 147.4
  - DIC(RE-MR) = 144.88

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Network Meta-Analysis - conclusions

- Only considered **binary outcomes** but NMAs can be implemented on many different data types using:
  - different **distributional assumptions**
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  - **link functions**
- Focus on **Bayesian** NMA methods through the `R` package `multinma` but corresponding **frequentist** methods can be obtained using the `R` package `netmeta`
- In presence of **disconnected** networks, ie ,alternative methods called **population-adjusted analyses** may be used to derive **unanchored** estimates:
  - *Matching Adjusted Indirect Comparison* (MAIC)
  - *Simulated Treatment Comparison* (STC)
  - require **IPD data** from at least one study

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Section 4

Reporting of CEAs

Results: base-case analysis

- **Costs** & **Effects** :
  - *Absolute* & *incremental* estimates with CIs
  - *Absolute* & *incremental* costs by cost category and total sums
  - *Absolute* & *incremental* QoL by health state (if applicable)

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- **CE quantities** :
  - **Incremental Cost-Effectiveness Ratio** : ICER $= \frac{\Delta_c}{\Delta_e}$
  - **Net Monetary Benefit** : NMB $= k \times \Delta_e - \Delta_c$

    Use **reference CE threshold** k –> **CE in practice Manual**

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  - **Net Monetary Benefit** : NMB $= k \times \Delta_e - \Delta_c$

    Use **reference CE threshold** k –> **CE in practice Manual**
- **Subgroup analyses** (if applicable):
  - All CE results *presented separately* for each subgroup

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Results: sensitivity analyses

- **Deterministic** & **scenario** analyses (*model-based*):
  - Chosen parameter distribution
  - ICER and incremental quantities lower/upper values
  - Always compared with base-case results

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    Cost-Effectiveness Plane (*CE plane*)
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    Cost-Effectiveness Acceptability Curve (*CEAC*)
- **Value of Information** analyses (*model-based*):
  - **Expected Value of (Partial) Perfect Information** (*EV(P)PI*) plot
  - EVSI and ENBS results may be presented –> **VoI analyses Manual**

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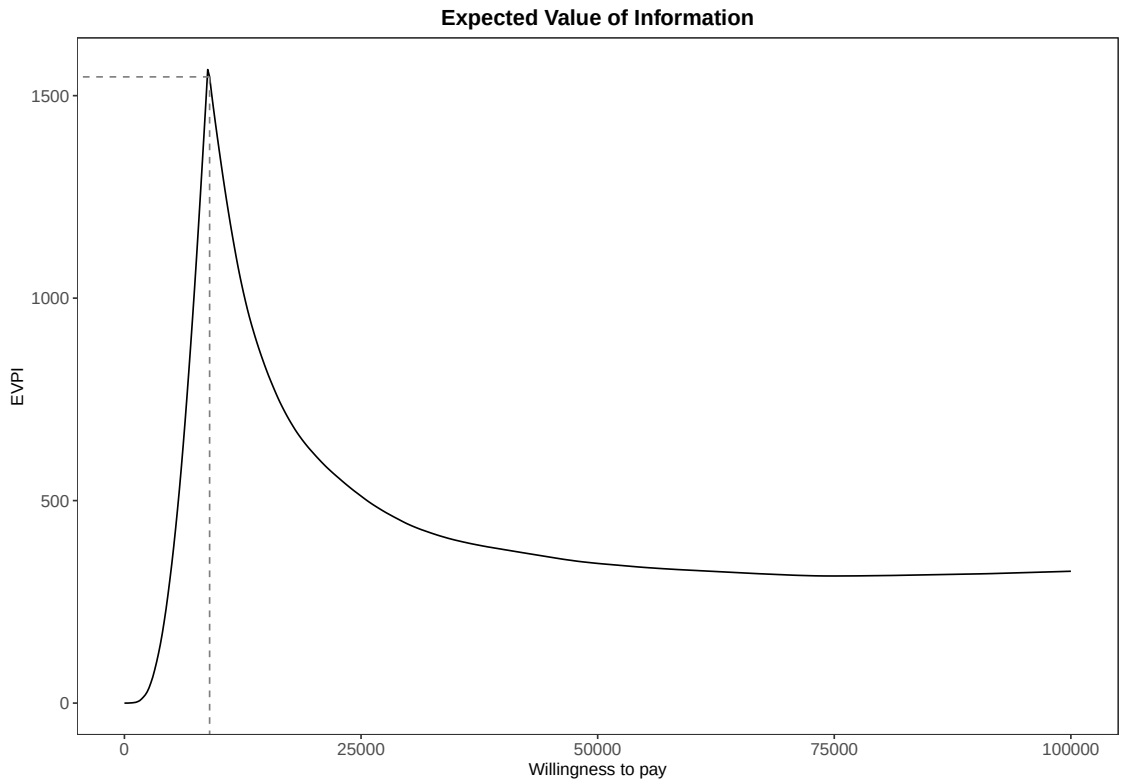
Results: VoI analysis - example

- **EVPI** = expected value of *perfect* information across all modelled aspects of decision problem $\rightarrow$ see voi
  - equal to the **expected costs** of uncertainty with making the decision based on the current **imperfect** evidence
  - *risk criterion* which shows the **consequences** of uncertainty



Section 5

Conclusions

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- Model-based analysis often used to inform HTA decisions but there remain strong concerns with their **credibility**

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  - **conceptualisation** of the model (eg perspective, time horizon, population) before observing the data
  - choice of **modelling technique** based on the context
  - parameter estimation and **uncertainty quantification**
  - **transparency** & **validation**

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- Relative simple models (eg DTs and cohort MMs) **attractive** but may rely on too **strong assumptions** in some case, where alternative **more flexible** approaches should be used, eg *individual-level microsimulation* methods

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Summary

- Model-based analysis often used to inform HTA decisions but there remain strong concerns with their **credibility**
- Guidelines for **good practices** in modelling should be followed:
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- Relative simple models (eg DTs and cohort MMs) **attractive** but may rely on too **strong assumptions** in some case, where alternative **more flexible** approaches should be used, eg *individual-level microsimulation* methods
- Important to identify **barriers** and **facilitators** of methods

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R you still using Excel/SPSS?

R you still using Excel? (Incerti et. al 2019)

- Historically, HTAs conducted with **commercial software** (eg SPSS) or **spreadsheet software** (eg Excel) which:
  - Are sufficient for simple analyses **BUT**
  - Put **constraints** that limit credibility and relevance
- **Modern programming languages** (eg R) facilitate the development of models that are:
  - Increasingly sophisticated and realistic
  - Capable of quantifying decision **uncertainty**
  - Tansparent and reproducible
  - Reusable and adaptable
- **R** user/developer communities well suited to:
  - Develop/implement HTA models in a **single software environment**
  - Catch up with **methodological advances**
  - Spot and correct code errors via **open-source** nature of packages

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A path forward for HTA

- Still a general lack of **software experience** in the HTA community:
  - *Insufficient* training in script-based prog software
  - *Limited* guidance on how to implement standard models
- Critical to **train** the next generation of health economists in *state of the art* methods and *software* to implement them
- **How to do this**?
  - Developing university *courses* & *workshops*
  - Writing *tutorial papers*
  - Making code *freely available* on repositories (eg *GitHub*)
  - *Encouraging* the use of programming languages among researchers

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Section 6

Appendix - R code

Appendix - resources for code and methods

- Full code available **@AnGabrio GitHub**
- **Empirical Analyses**:
  - `HSR_2025_v1.pdf` presentation
  - `code.html` description of methods and `R` code
  - `code_functions.R` custom `R` code functions
  - `example.R` fake example to implement code
  - added examples & functions to combine MI and bootstrapping
- **Model-Based Analyses**:
  - `HSR_2025_v2.pdf` presentation
  - `code2.html` description of *presented* methods and `R` code
  - `code3.html` description of *additional* methods and `R` code
  - original full code from online book **R for HTA Assessment**

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