

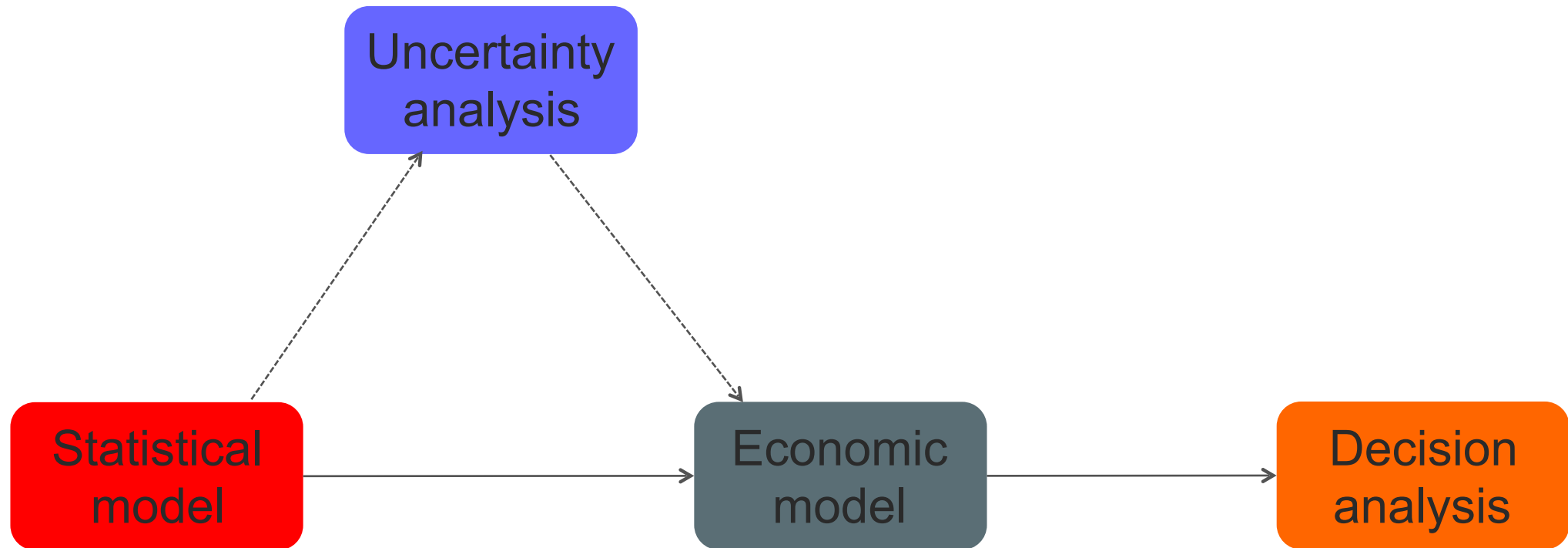
# Developing relevant economic models with R for health technology assessment

Devin Incerti

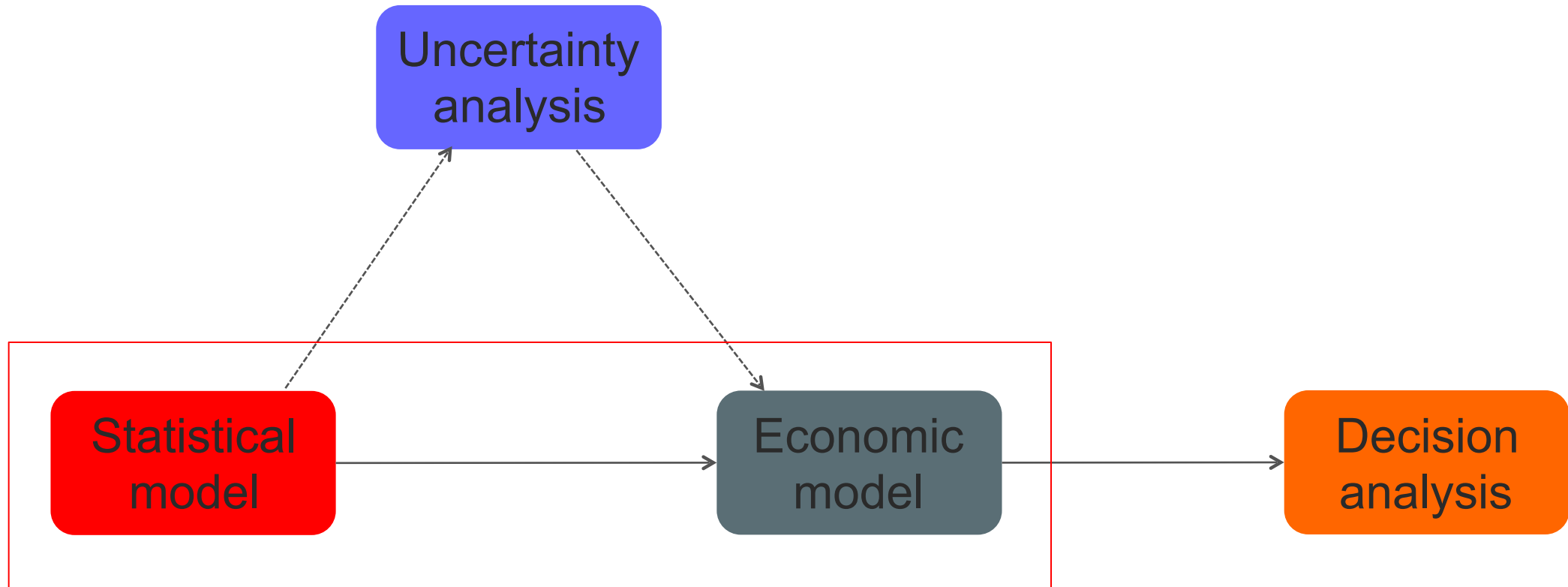
# What is a relevant model?

- > Based on available clinical evidence
- > Quantifies decision uncertainty
- > Transparent and reproducible
- > Reusable and adaptable

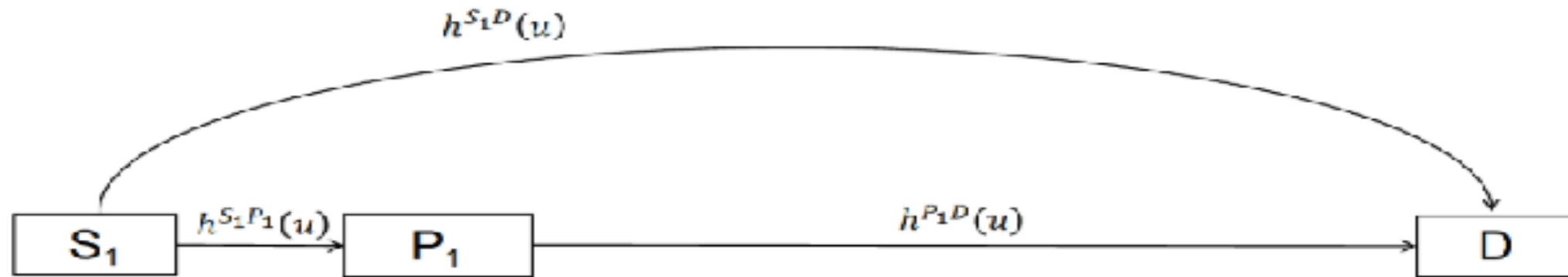
# Building an economic model for decision analysis



# Building an economic model for decision analysis



# Example: a multi-state model in oncology



> 3 health states

1. S1: Stable disease
2. P1: Progressed disease
3. D: Death

> 3 transitions where  $h^{rs}(u)$  is the time-varying hazard for transitions from state  $r$  to  $s$  as a function of time  $u$

1. Stable -> Progression
2. Stable -> Death
3. Progression -> Death

# Parameterizing multi-state models

Statistical method	R package	Data
Network meta-analysis	rjags/rbugs/rstan	Summary data from RCTs
Parametric & spline models	flexsurv	Continuously observed processes
Non-parametric and semi-parametric models	mstate	Continuously observed processes
Exponential and piecewise exponential models	msm	Panel data

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## Multi-state data with continuously observed processes

```
> head(mstate_data)
  patient_id strategy_id from to  Tstart  Tstop  years status trans
1:         1          1   1  2 0.020000 4.292950 4.292950      1     1
2:         1          1   1  3 0.020000 4.292950 4.292950      0     2
3:         1          1   2  3 4.292950 9.872690 5.579740      1     3
4:         2          1   1  2 0.020000 2.762491 2.762491      1     1
5:         2          1   1  3 0.020000 2.762491 2.762491      0     2
6:         2          1   2  3 2.762491 5.355236 2.592745      1     3
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```

## Fitting a multi-state Weibull model with flexsurv

```
fit_wei <- flexsurv::flexsurvreg(Surv(years, status) ~
  factor(strategy_id) * trans +
  shape(trans),
  data = mstate_data,
  dist = "weibull")
```



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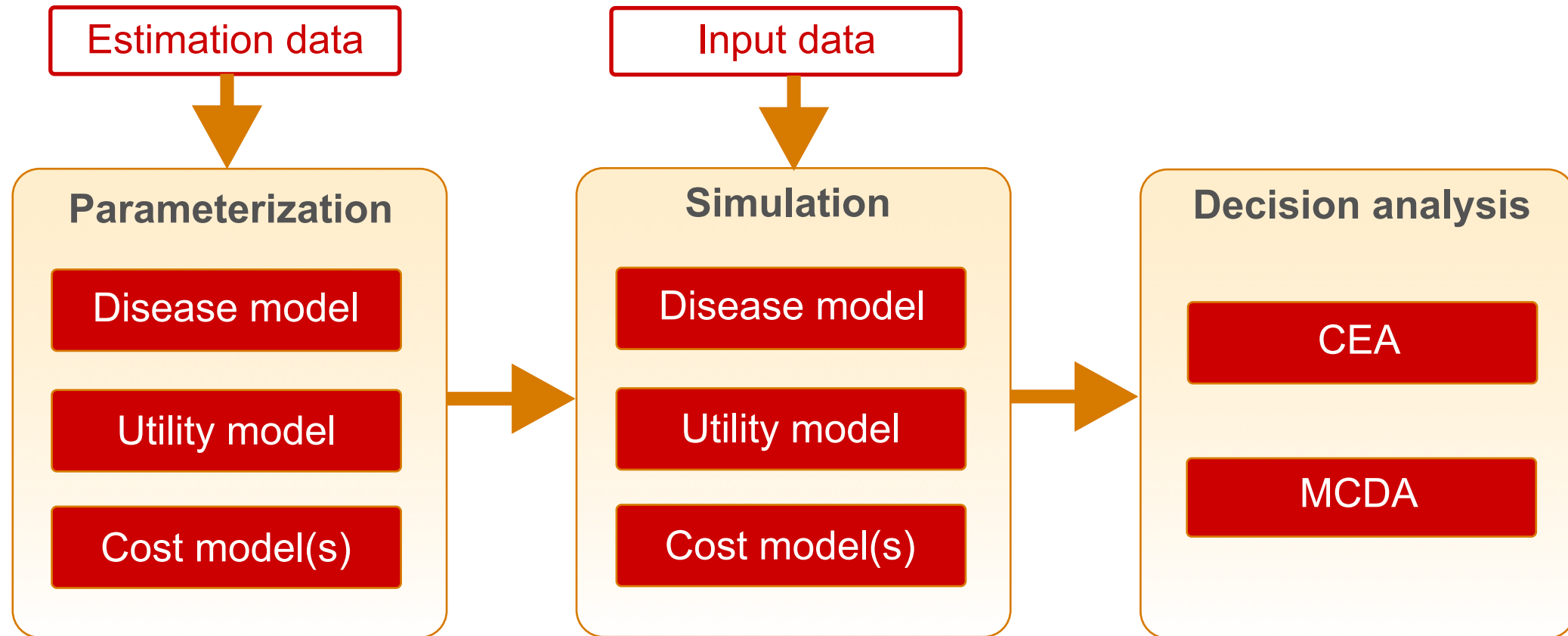
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  shape(trans),
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```

A "clock reset"  
model

# hesim: a new R package for integrating statistical and economic models for decision analysis



Economic models are constructed by combining statistical models for disease progression, utility, and costs. Disease progression, QALYs, and costs are simulated, which are used for decision analysis

# Simulating an economic model

- > Individual continuous time state transition models (*iCTSTMs*) can be used to simulate “clock-reset” multi-state models in *hesim*
- > Disease progression, utilities and costs simulated as function of *input data* and *parameters*

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## Input data for disease model

	strategy_id	patient_id	transition_id	age	female	from	to	from_name	to_name	trans
1:	1	1	1	40.94603	1	1	2	Stable	Progressed	1
2:	1	1	2	40.94603	1	1	3	Stable	Dead	2
3:	1	1	3	40.94603	1	2	3	Progressed	Dead	3
4:	1	2	1	29.85044	1	1	2	Stable	Progressed	1
5:	1	2	2	29.85044	1	1	3	Stable	Dead	2

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## Input data for disease model

```
strategy_id patient_id transition_id age female from to from_name to_name trans
1: 1 1 1 1 40.94603 1 1 2 Stable Progressed 1
2: 1 1 1 2 40.94603 1 1 3 Stable Dead 2
3: 1 1 1 3 40.94603 1 2 3 Progressed Dead 3
4: 1 1 2 1 29.85044 1 1 2 Stable Progressed 1
5: 1 1 2 2 29.85044 1 1 3 Stable Dead 2
```

## Parameters for disease model

```
Estimates:
              data mean  est    L95%    U95%    se    exp(est)  L95%    U95%
shape              NA    0.8274  0.7801  0.9779  0.0706    NA      NA      NA
scale              NA    5.2865  3.9219  7.1258  0.8053    NA      NA      NA
factor(strategy_id)2  0.4834  0.2084 -0.2959  0.6966  0.2532  1.2218  0.7438  2.0070
trans2              0.3992  0.9847  0.4685  1.5010  0.2634  2.6771  1.5976  4.4851
trans3              0.2016 -0.2770 -0.6554  0.1014  0.1931  0.7581  0.5192  1.1057
factor(strategy_id)2:trans2  0.2035 -0.9044 -1.5706 -0.2381  0.3399  0.4048  0.2079  0.7881
factor(strategy_id)2:trans3  0.0763 -0.4157 -1.0671  0.2357  0.3324  0.6599  0.3440  1.2658
shape(trans2)       0.3992  0.6986  0.3688  1.0275  0.1678  2.0110  1.4474  2.7939
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## Parameters for disease model

Estimates:

	data	mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape	NA	NA	0.8274	0.7201	0.9779	0.0706	NA	NA	NA
scale	NA	NA	5.2865	3.9219	7.1258	0.8053	NA	NA	NA
factor(strategy_id)2	0.4834	0.2084	-0.2959	0.6966	0.2532	1.2218	0.7438	2.0070	
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## Simulated disease progression

	sample	strategy_id	patient_id	from	to	final	time_start	time_stop	
1:	1	1	1	1	2	0	0.0000000	0.6540819	
2:	1	1	1	1	2	3	1	0.6540819	1.6727070
3:	1	1	1	2	1	3	1	0.0000000	2.5778704
4:	1	1	1	3	1	2	0	0.0000000	0.6408648
5:	1	1	1	3	2	3	1	0.6408648	7.3911212
6:	1	1	1	4	1	2	0	0.0000000	1.9094159

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Uncertainty in parameters propagated to uncertainty in disease progression via PSA

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Uncertainty in parameters propagated to uncertainty in disease progression via PSA

R code is a wrapper for underlying C++, which makes PSA with microsimulation fast



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- > Economic model combines disease model (i.e., transition model for iCTSTM), utility model, and cost models

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econmod$sim_disease()  
econmod$sim_qalys(dr = .03)  
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ecpnmod$sim_costs(dr = .03)
```

- > And can be used for cost-effectiveness analysis

```
# with hesim  
ce <- econmod$summarize()  
icea <- icea(ce, dr = .03)  
icea_pw <- icea_pw(ce, dr = 0.03,  
                  comparator = 2)
```

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econmod$sim_qalys(dr = .03)  
econmod$sim_costs(dr = .03)
```

- > And can be used for cost-effectiveness analysis

```
# with hesim  
ce <- econmod$summarize()  
icea <- icea(ce, dr = .03)  
icea_pw <- icea_pw(ce, dr = 0.03,  
                  comparator = 2)
```

```
# with BCEA  
qalys_mat <- matrix(ce$qalys$qalys, nrow = n_samples,  
                   byrow = TRUE)  
costs_mat <- matrix(ce$costs$costs, nrow = n_samples,  
                   byrow = TRUE)  
bcea <- BCEA::bcea(e = qalys_mat, c = costs_mat,  
                  ref = 2)
```

# Making models reproducible with R Markdown

## 3.2 Constructing the model

We construct the economic model by combining the separate models for the health state transitions, utility, and costs.

```
n.samples <- 100
```

### 3.2.1 Health state transition model

Health state transitions are simulated as a function of input data (which contains the covariates from the multi-state model describing differences in transition rates across treatments) and parameters (the coefficients from the multi-state NMA). These are automatically created as a function of the model structure, transition matrix, and patient population with `create_transmod_data()` and stored below in a data table named `transmod_data`. A fraction of patients are T790M mutation positive (and this fraction can vary across treatments). Coefficients from the multi-state NMA that are contained in `transmod_data` are extracted using `transmod_params()`.

Recall from the discussion above that an individual-level model is required to simulate a CTSTM that that is a mixture of clock-reset and clock-forward approaches. A model of health state transitions for an individual-level CTSTM (ICTSTM) can be constructed with the `IndivCtstmTrans` class in `hesim`.

```
# Input data
transmod_data <- create_transmod_data(struct, tmat, pats)
## Print first 5 rows and one ID covariate from data
print(transmod_data[1:5, 1:14])

##   strategy_id patient_id transition_id female   age mutation tx Abb
## 1:           1           1             1    0 76.00278    1  er1
## 2:           1           1             2    0 76.00278    1  er1
## 3:           1           1             3    0 76.00278    1  oci
## 4:           1           1             4    0 76.00278    1  oci
## 5:           1           1             5    0 76.00278    1  oci
##   tx_hist osi_s1p1_scale osi_s1d_scale
## 1:  -NA-              1              0
## 2:  -NA-              0              1
## 3:   er1              0              0
## 4:   er1              0              0
## 5:   er1              0              0

# Parameters
transmod_params <- create_transmod_params(n = n.samples, data = transmod_data)
## Print first 5 samples from the probability distribution and 4 covariates (which
## match those in 'transmod_data')
transmod_params$params[scales][1:5, 1:4]

##   osi_s1p1_scale d_er1_s1p1_scale f_per_s1p1_scale osi_s1d_scale
## [1,]           2                -1                -6.5           0
## [2,]           2                -1                -6.5           0
## [3,]           2                -1                -6.5           0
## [4,]           2                -1                -6.5           0
## [5,]           2                -1                -6.5           0

# Health state transition model
transmod <- hesim::create_IndivCtstmTrans(transmod_params, transmod_data, tmat,
                                         start_age = pats$age)
class(transmod)
```

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3.3 Simulation

4 Decision analysis

4.1 Cost-effectiveness analysis

4.2 Multi-criteria decision analysis

5 Value of hope



# Making models reproducible with R Markdown

```
## Constructing the model
```

We construct the economic model by combining the separate models for the health state transitions, utility, and costs.

```
```{r}
n_samples <- 100
```
```

```
### Health state transition model
```

Health state transitions are simulated as a function of input data (which contains the covariates from the multi-state model describing differences in transition rates across treatments) and parameters (the coefficients from the multi-state NMA). These are automatically created as a function of the model structure, transition matrix, and patient population with `create_transmod_data()` and stored below in a data table named `transmod_data`. A fraction of patients are T790M mutation positive (and this fraction can vary across treatments). Coefficients from the multi-state NMA that are contained in `transmod_data` are extracted using `transmod_params()`.

Recall from the discussion above that an individual-level model is required to simulate a CTSTM that that is a mixture of clock-reset and clock-forward approaches. A model of health state transitions for an individual-level CTSTM (iCTSTM) can be constructed with the `IndivCtstmTrans` class in `hesim`.

```
```{r}
# Input data
transmod_data <- create_transmod_data(struct, tmat, pats)
## Print first 5 rows and and 10 covariates from data
print(transmod_data[1:5, 1:10])

# Parameters
transmod_params <- create_transmod_params(n = n_samples, data = transmod_data)
## Print first 5 samples from the probability distribution and 4 covariates (which
## match those in 'transmod_data')
transmod_params$coefs$scale[1:5, 1:4]
```

# Increasing transparency with web apps

- > Web apps can be built using R Shiny or by embedding R code into JavaScript
- > Allows users to run custom analyses without any knowledge of R

The screenshot displays the 'M-FA Model Interface' web application. It features a dark sidebar on the left with navigation options: Introduction, Setup model, Population, Treatment sequences, Model structure (selected), Parameter values, Run simulation, View inputs used in simulation, View model results, More information, and Terms and conditions. The main content area is divided into four panels:

- Initial treatment phase (first 6 months)**
  - Relationship between treatment and HAQ
    - Treatment → ACR → HAQ
    - Treatment → ACR → EULAR → HAQ
    - Treatment → HAQ
  - Relationship between treatment and switching to a new treatment
    - Treatment → ACR → Switch
    - Treatment → ACR → ΔDAS28 → DAS28 → Switch
    - Treatment → ACR → ΔSDAI → SDAI → Switch
    - Treatment → ACR → ΔCDAI → CDAI → Switch
    - Treatment → ΔDAS28 → DAS28 → Switch
    - Treatment → ACR → EULAR → Switch
- Time to treatment discontinuation**
  - Cause of treatment discontinuation
    - All causes
    - Serious infections only
  - Survival distribution used to model treatment duration
    - Exponential
    - Weibull
    - Gompertz
    - Gamma
    - Log-logistic
    - Lognormal
    - Generalized gamma
- HAQ progression in the absence of tDMARDs**
  - HAQ progression model
    - Latent class growth model (LCGM)
    - Constant linear progression
- Utility algorithm**
  - Mapping HAQ to utility
    - Hernandez-Alava (2013) mixture model ([link](#))
    - Wailoo (2006) logistic regression equation ([link](#))

# Tailoring web apps to different audiences

- > Web app for rheumatoid arthritis decision model aimed at general audience

The IVI-RA Value Tool   Welcome   **1. Setup**   2. Outcomes   3. Value   4. Explore   About

## Get started by answering a few questions

The IVI-RA Value Tool simulates the average lifetime value of treatments for a population of patients with moderate to severe RA. The results of the simulation depend on a number of factors including the characteristics of the patient population, the treatments used, and the costs of drugs. Setup the model below.

[Reset defaults](#)

### RA patient population

The value of RA treatments depends on the characteristics of the patients in the treated population – their age, for example. The IVI-RA Value Tool uses a nationally representative RA population by default, but you can make adjustments here. Would you like to adjust to reflect a specific population?

- Pick for me
- I want to make adjustments

### Sequences of RA treatments to compare over patients' lifetimes

The IVI-RA Value Tool examines treatments over patients' lifetimes, which is important because RA patients often switch therapies when they stop working. The treatment sequence followed by each individual patient in the simulation will match one of the sequences selected here, and all results compare the outcomes of these sequences relative to one another. Would you like to enter your own customized treatment sequences?

- Pick for me
- I want to customize treatment sequences to compare

### Treatment costs

An important input into value is the cost of a drug. Do you want to choose drug costs, or would you prefer that we use default values instead?

- Pick for me
- I want to choose

[I'm ready to run the model and see results](#)

# So why R?

- > A comprehensive ecosystem for fitting statistical models
- > Computational efficiency
- > Reproducible research
- > Web apps
- > Unit testing

## *Live Content Slide*

*When playing as a slideshow, this slide will display live content*

**Poll: Following our presentations, how much more likely are you to start using R for decision modelling?**

# Resources

- > Gianluca's R packages

- > <https://github.com/giabaio>

- > [http://www.statistica.it/gianluca/page\\_software/](http://www.statistica.it/gianluca/page_software/)

- > Toy decision tree model

- > <https://github.com/Bogdasayen/Depression-toy-decision-tree-in-R>

- > hesim

- > <https://innovationvalueinitiative.github.io/hesim/>

- > IVI-RA Web apps

- > Expert (<https://innovationandvalueinitiative.shinyapps.io/ivi-ra-expert/>)

- > General audience (<https://innovationandvalueinitiative.shinyapps.io/ivi-ra/>)

**IVI**



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