An open-source cost-effectiveness simulation model for rheumatoid arthritis in R

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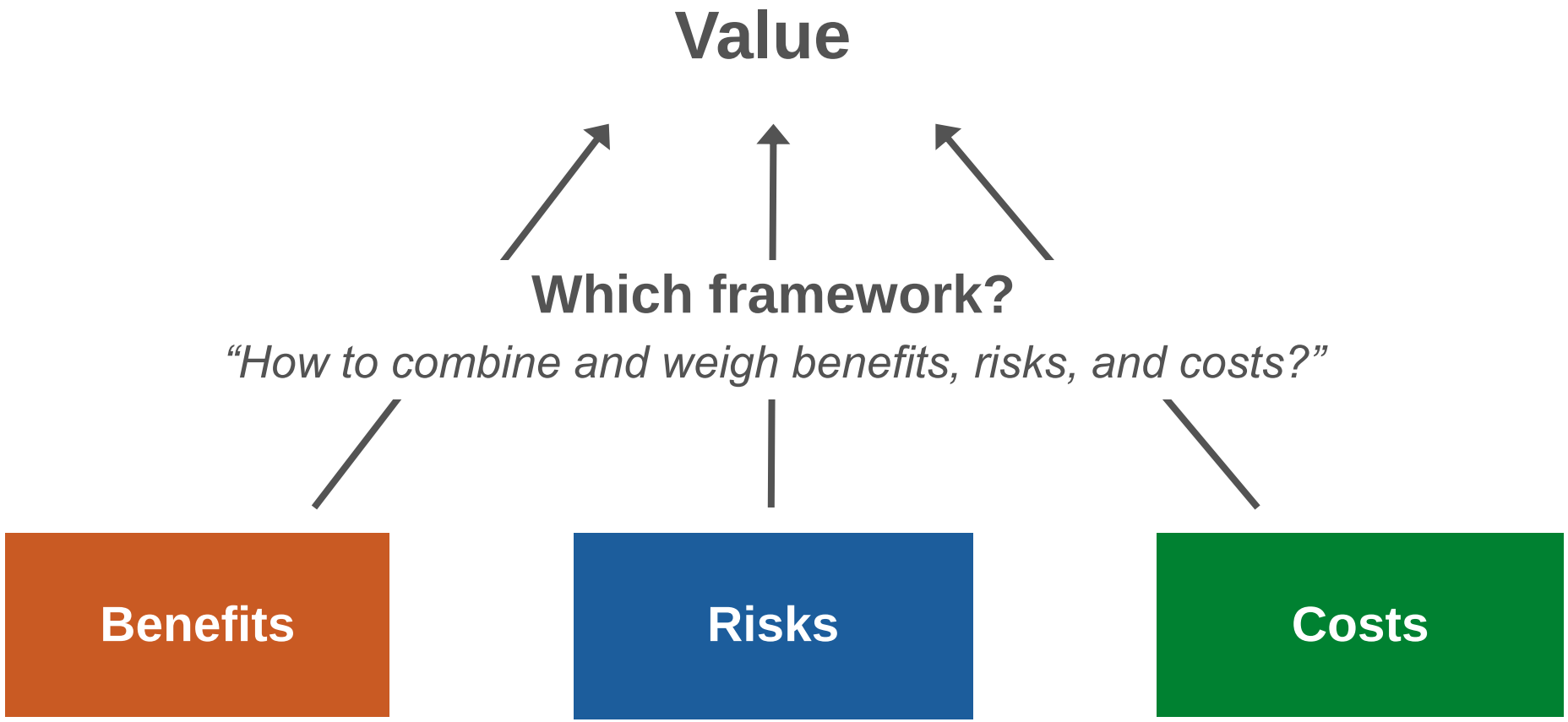
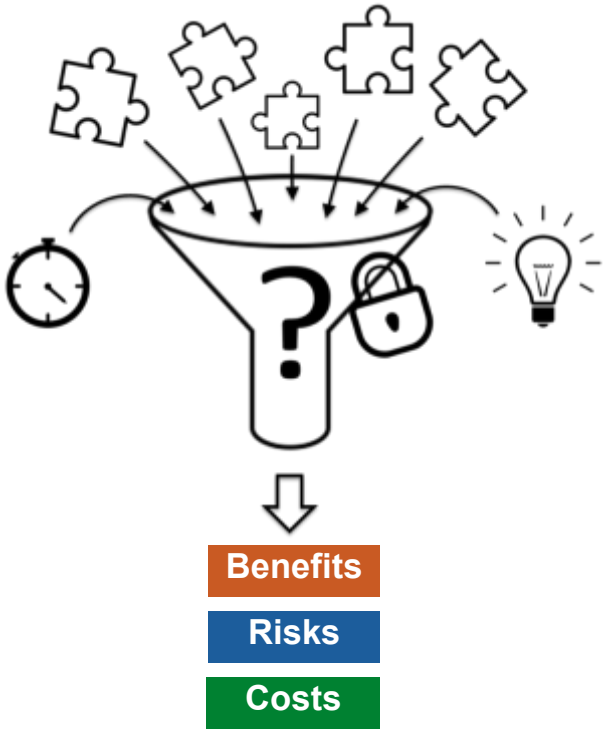
Value assessment? Yes, but how?



How to calculate the benefits, risks, and costs used in the value assessment?

Credibility and *Relevance* of published model-based assessments of value?

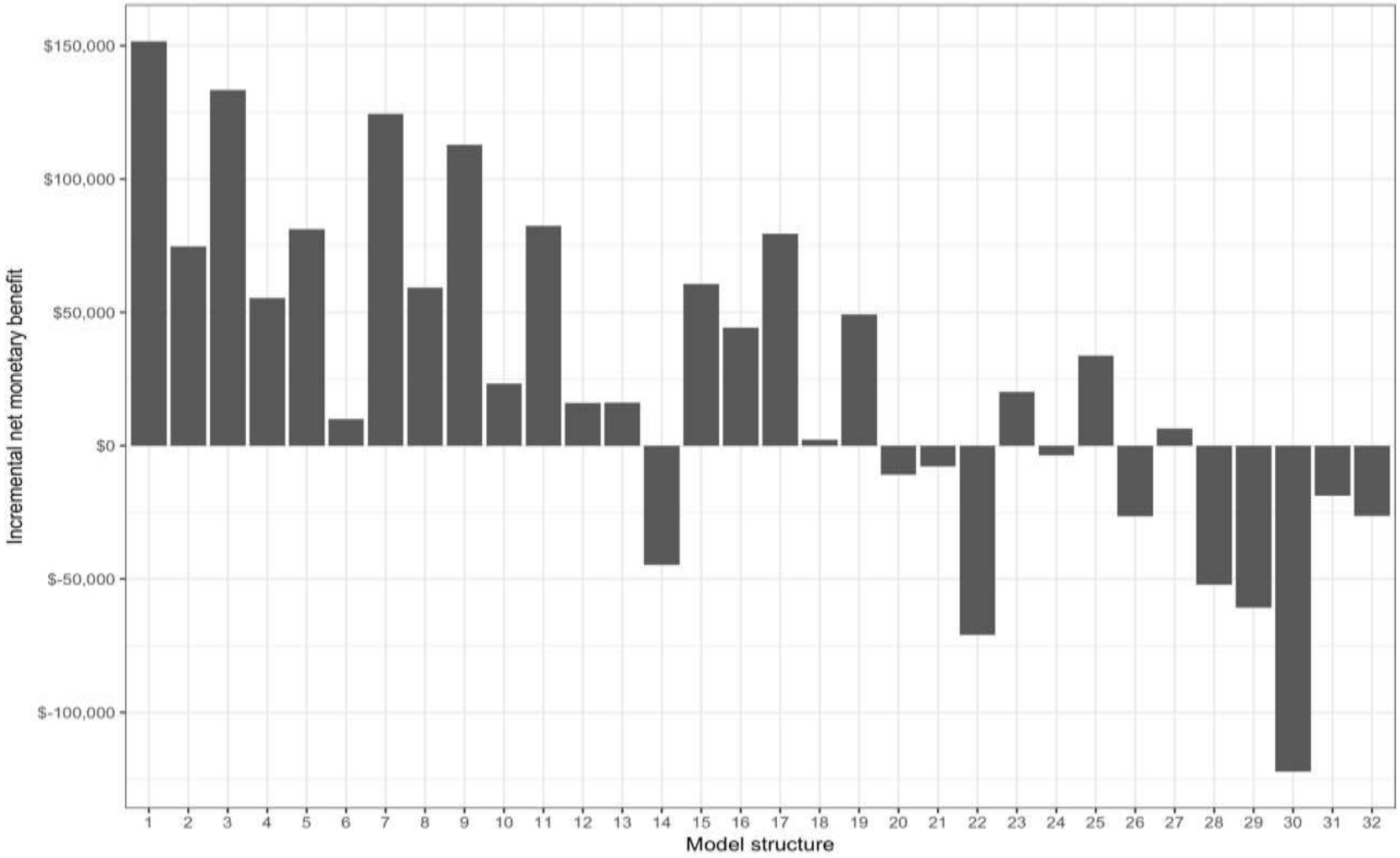
- Lack of transparency
- Idiosyncratic choices regarding model structure having an impact on findings
- Conflict of interest?



- Perceived as complex; difficult to understand by decision-makers
- Quickly outdated given pace of new clinical evidence
- Cumbersome, if not impossible, for someone other than the original model developer to update the analysis

Structural uncertainty

Sensitivity of findings to 32 competing structural assumptions in IVI-RA model. Incremental net-monetary benefit (at WTP of 150,000 US$) with sequential targeted DMARD treatment relative to conventional DMARD treatment



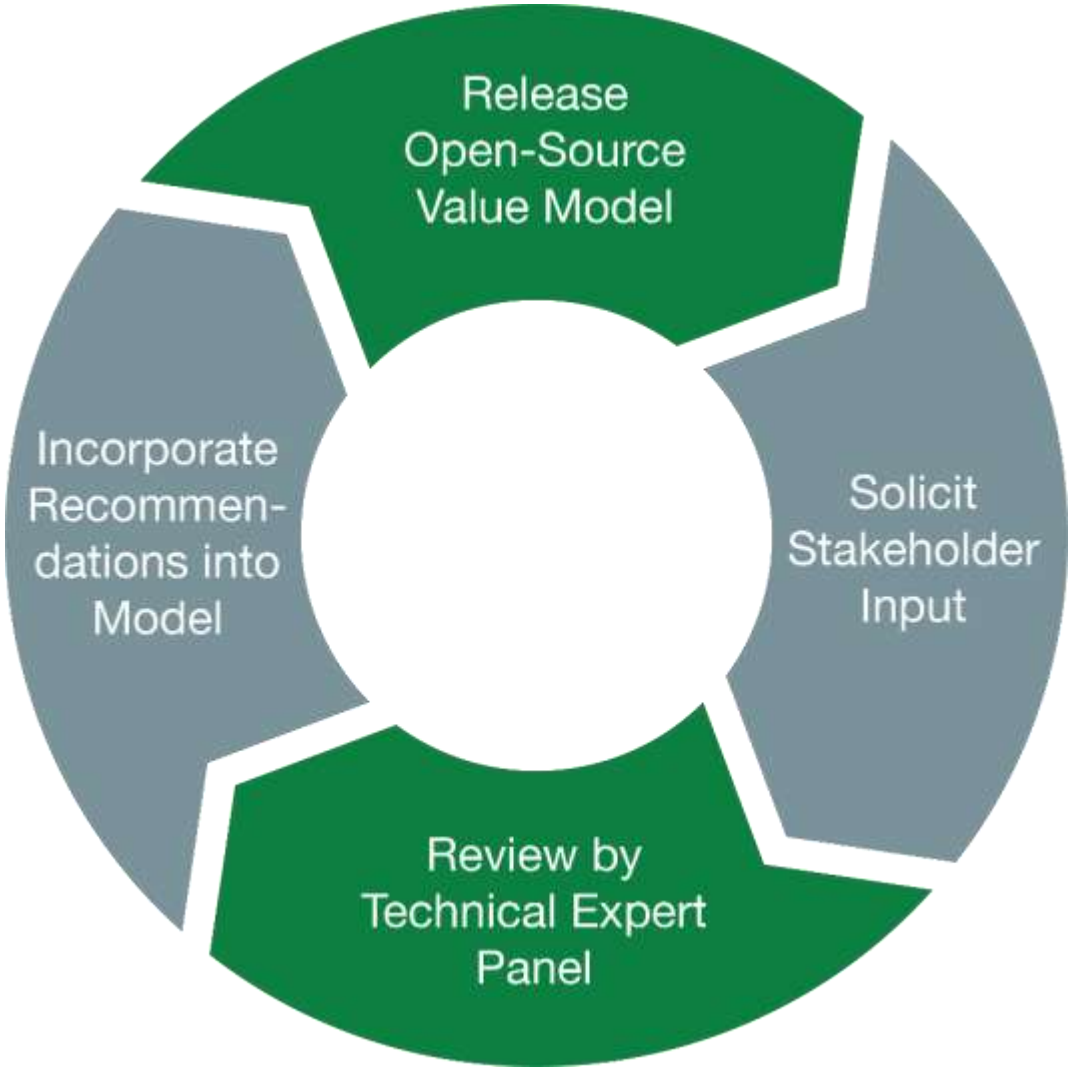
Open Source Value Project (OSVP)

> Development of flexible open-source models for value assessment

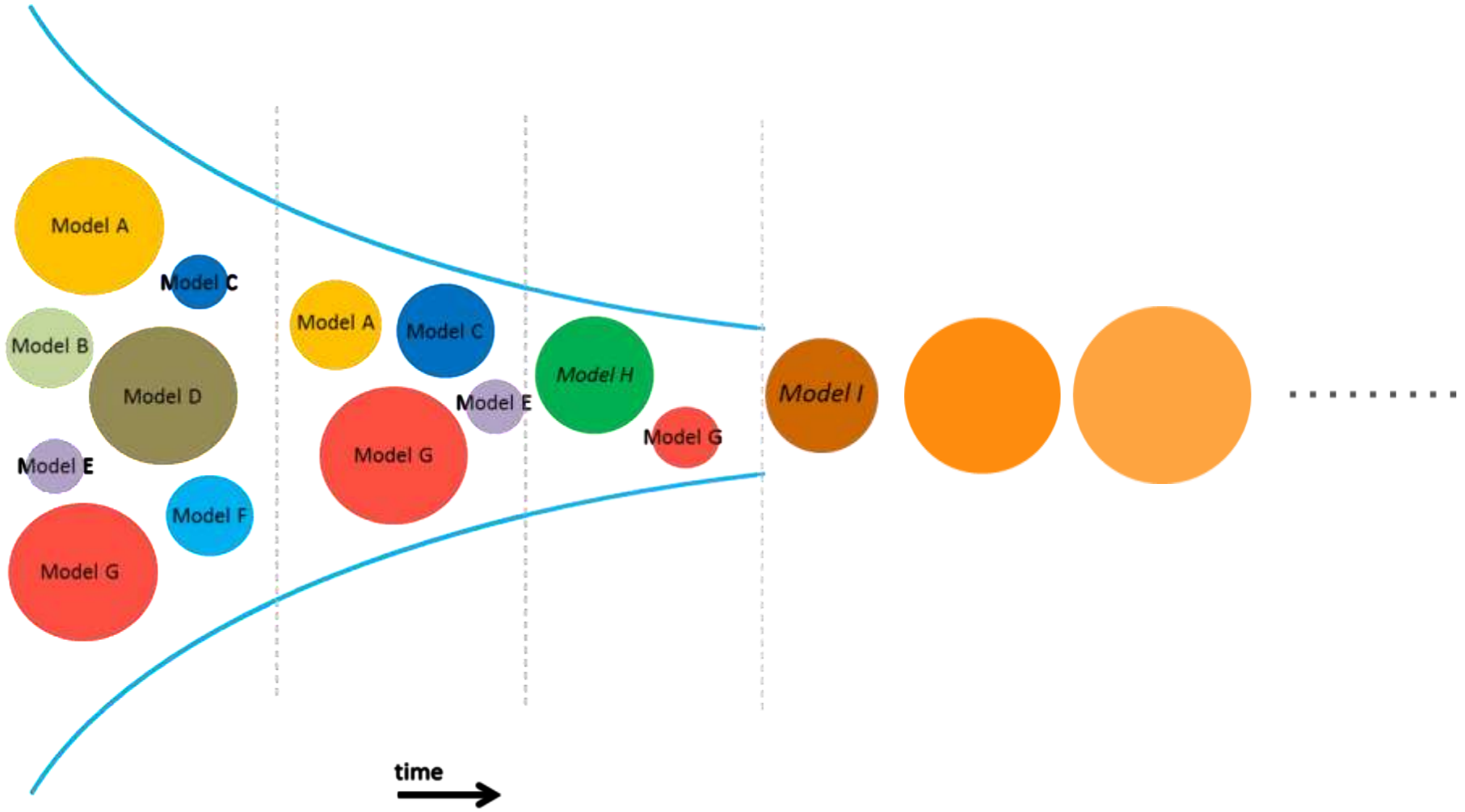
1. To enable a more constructive dialogue between stakeholders with different beliefs about relevant clinical data, modeling approaches, and value perspectives

2. To provide local decision-makers with means to credible value assessment that reflects the local setting and is based on the latest evidence while accounting for all scientific uncertainty (due to patient heterogeneity, gaps in evidence, and different modeling beliefs)

Open-source, collaborative, iterative



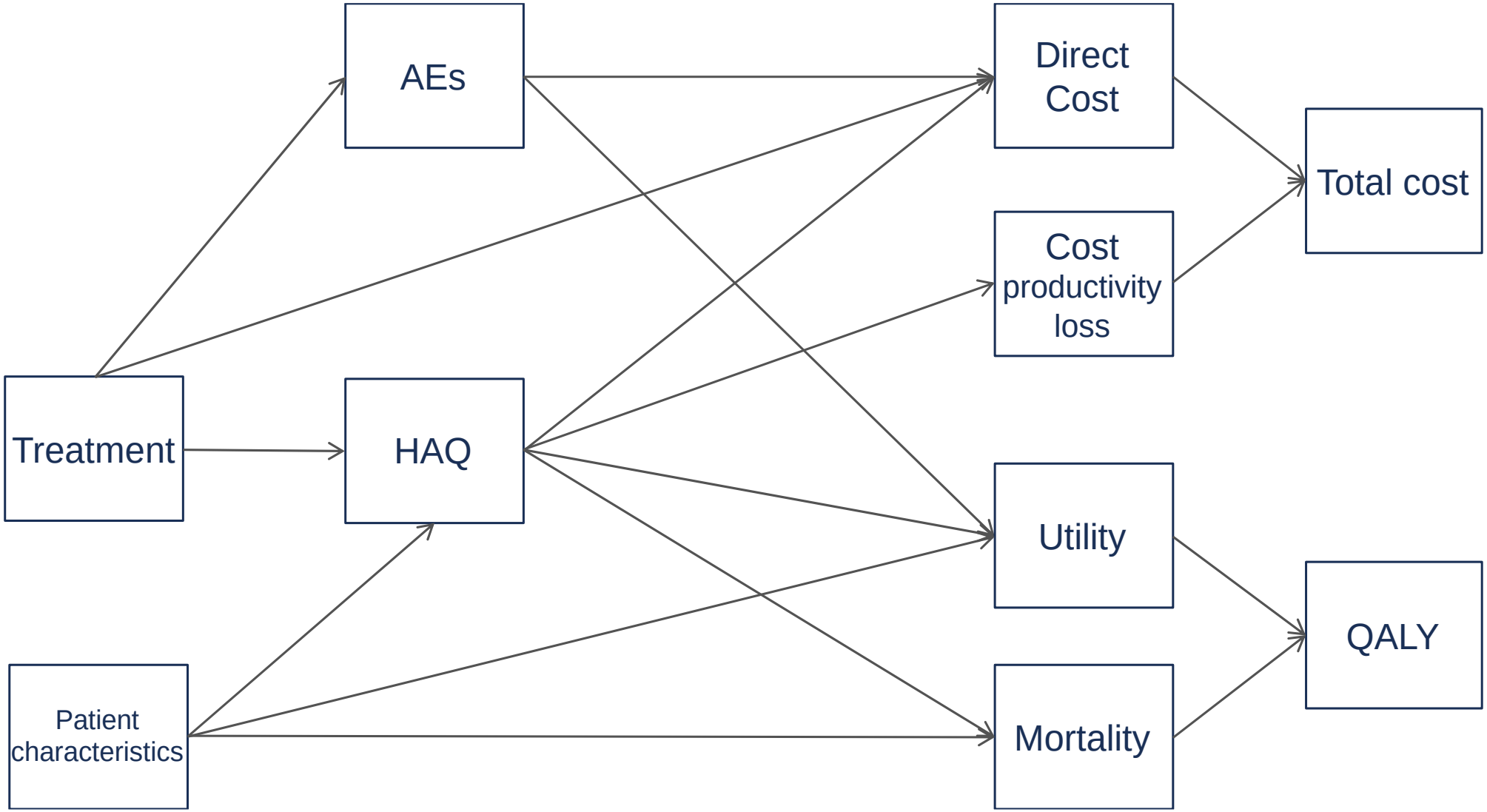
Crowd-sourcing expertise & model averaging



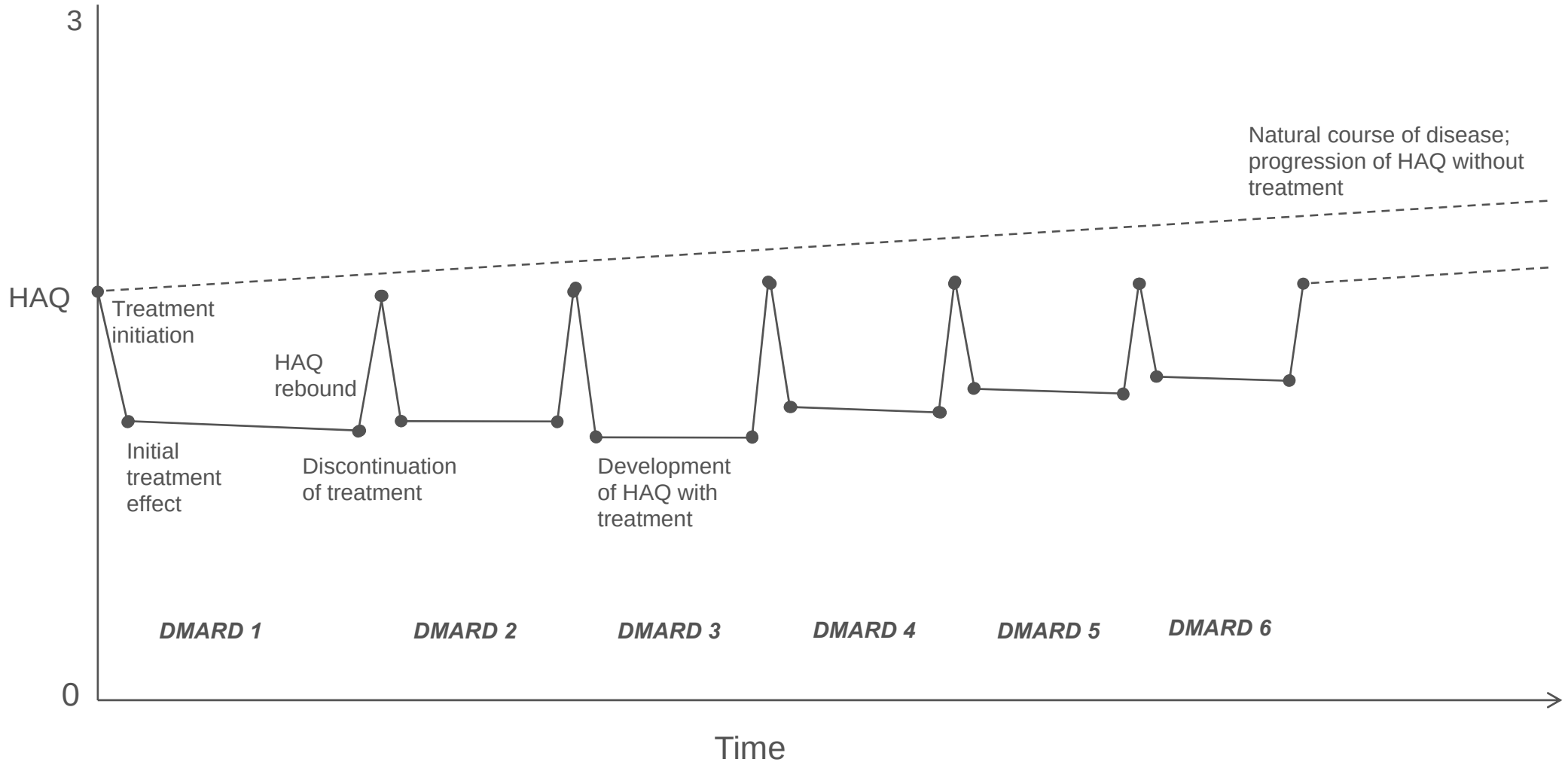
IVI-RA model

- Open source decision model to assess the value of different (sequences of) conventional and targeted disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis (RA)
  - CEA and MCDA
- Discrete-time individual patient simulation with 6 month cycles
- Accounts for both parameter and structural uncertainty
- Model input parameters based on the literature
- Competing model structures were informed by existing cost-effectiveness models and clinical expertise

Influence diagram



Development of HAQ over time

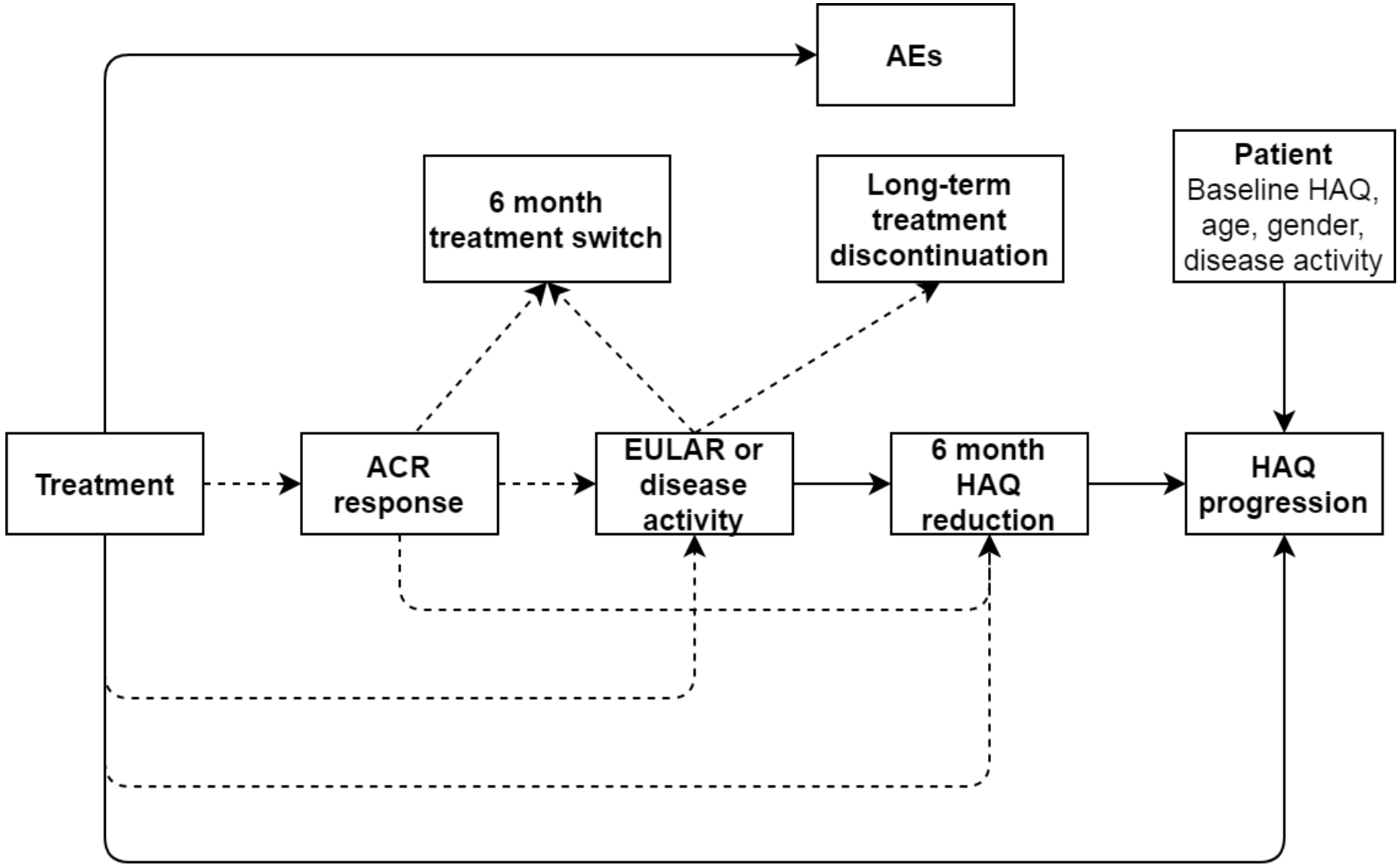


Competing model structures

300+ possible model structures

- short-term effect of treatment on HAQ
- causes of treatment switching
- long-term progression of HAQ
- the probability distribution for time to treatment discontinuation
- algorithm used to simulate utility

Alternative structural assumptions regarding the impact of treatment on HAQ and switching



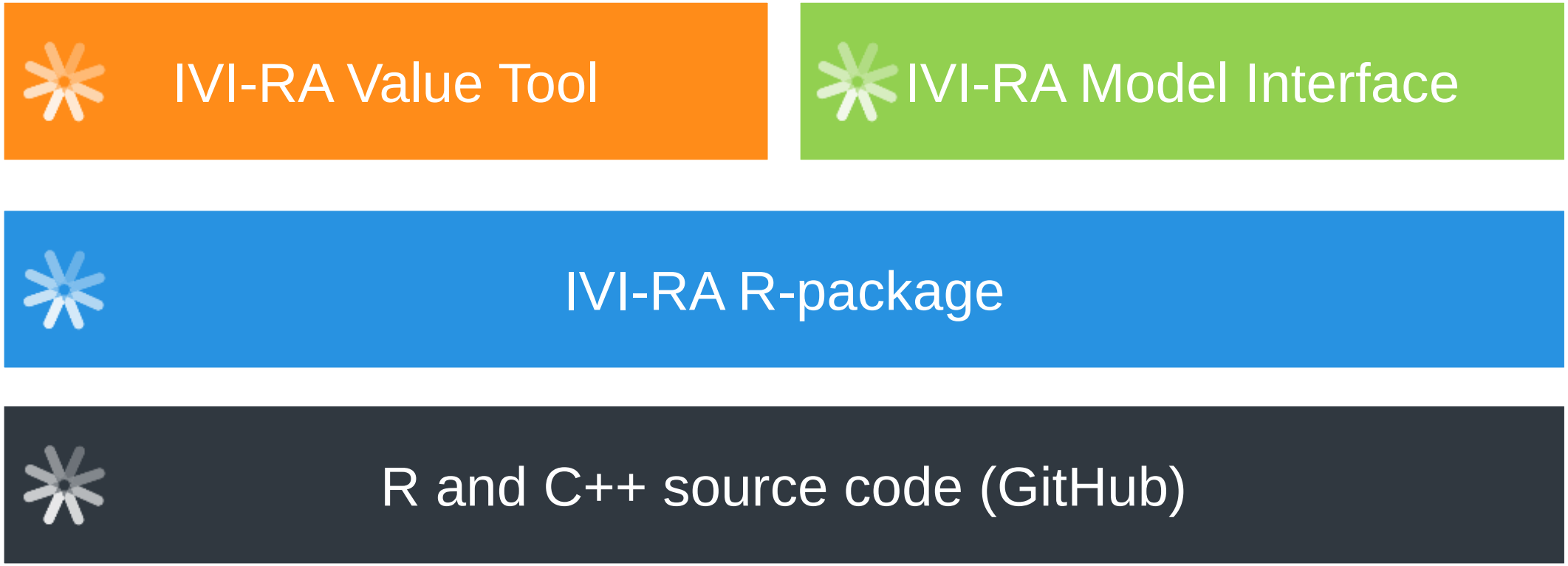
Source data – Literature based

	RCT evidence	Routine practice, observational evidence	Other
Treatment effects at 6 months	ACR/ DAS28/ HAQ	Mapping between endpoints	
Long term treatment effects (6+ months)		HAQ trajectory over time	
Treatment duration		Corrona	
Adverse events	Serious infections		
Utility		HAQ -> EQ-5D	
Mortality		• US life tables • Impact of HAQ on mortality	
Resource use		• Physician visits, • Chest X-rays tuberculosis tests, outpatient visit • HAQ -> hospitalization	Drug regimen according FDA label
Productivity		HAQ -> productivity	

Model outcomes

- HAQ trajectory
- Time to treatment discontinuation by line of therapy
- Life-years
- QALYs
- Health care sector costs
  - Drug acquisition and administration; General management and monitoring; Adverse events; Hospitalization
- Non-health care sector costs
  - Productivity loss
- Total costs
- CEA and MCDA

IVI-RA model



innovationvalueinitiative.github.io/IVI-RA

Performance requirements

- Flexible models for decision analysis
  - Individual patient simulation
  - Probabilistic sensitivity analysis
  - Structural uncertainty analysis
  - Integration with web applications
- Computationally intensive
  - Run 10,000 individual patients
  - Sample 1,000 parameter sets for PSA
  - Consider 50 model structures
  - => 500,000,000 iterations
- Intensive code is therefore written in C++

Source code used to build…

Branch: master ▾ IVI-RA / src / ips.h Find file | Copy path

dincerti New unit test for c++ classes and functions 6f3af90 on Oct 21

1 contributor

110 lines (100 sloc) | 2.6 KB Raw | Blame | History

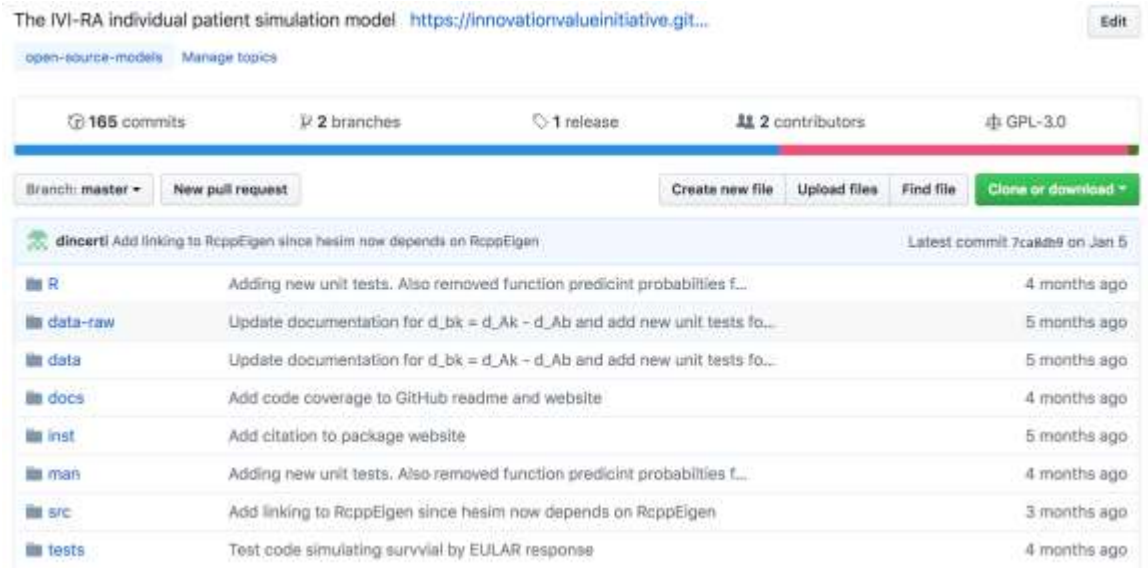
```
1   # ifndef ips_H
2   # define ips_H
3   #include <RcppArmadillo.h>
4
5   class nmaACR {
6   public:
7     std::string hist;
8     double k;
9     double A;
10    double z2;
11    double z3;
12    arma::rowvec d_beta;
13    arma::rowvec x;
14    void set(std::string hist_, double k_, double A_, double z2_, double z3_,
15             arma::rowvec d_beta_, arma::rowvec x_, int line);
16    arma::rowvec acrprobs();
17    double sim_acr();
18  };
19
```

…an R package

```
pop <- sample_pop(n = 10, type = "homog")
tx.seq <- c("adamtx", "cdmards")
mod.structs <- select_model_structures(tx_ihaq = c("acr-haq", "acr-eular-haq"),
                                       tx_iswitch = c("acr-switch", "acr-eular-switch"),
                                       cdmards_haq_model = c("lcgm", "linear"),
                                       ttd_cause = c("all", "si"),
                                       ttd_dist = c("gengamma", "exponential"),
                                       utility_model = c("mixture", "wailoo"))
input.dat <- get_input_data(pop = pop)
parsamp <- sample_pars(n = 10, input_dat = input.dat)
sim.out <- sim_iviRA(tx_seqs = tx.seq, input_data = input.dat, pars = parsamp,
                     model_structures = mod.structs, output = "data")
head(sim.out)
#>    model sim id month tx line tx_cycle death  age        ttd acr eular das28
#> 1:     1   1  1     6  3    1        1     0 55.0  3.5129569   3    NA    NA
#> 2:     1   1  1    12  3    1        2     0 55.5  2.5129569   3    NA    NA
#> 3:     1   1  1    18  3    1        3     0 56.0  1.5129569   3    NA    NA
#> 4:     1   1  1    24  3    1        4     0 56.5  0.5129569   3    NA    NA
#> 5:     1   1  1    30  3    1        5     0 57.0 -0.4870431   3    NA    NA
#> 6:     1   1  1    36  1    2        1     0 57.5  0.0000000   0    NA    NA
```

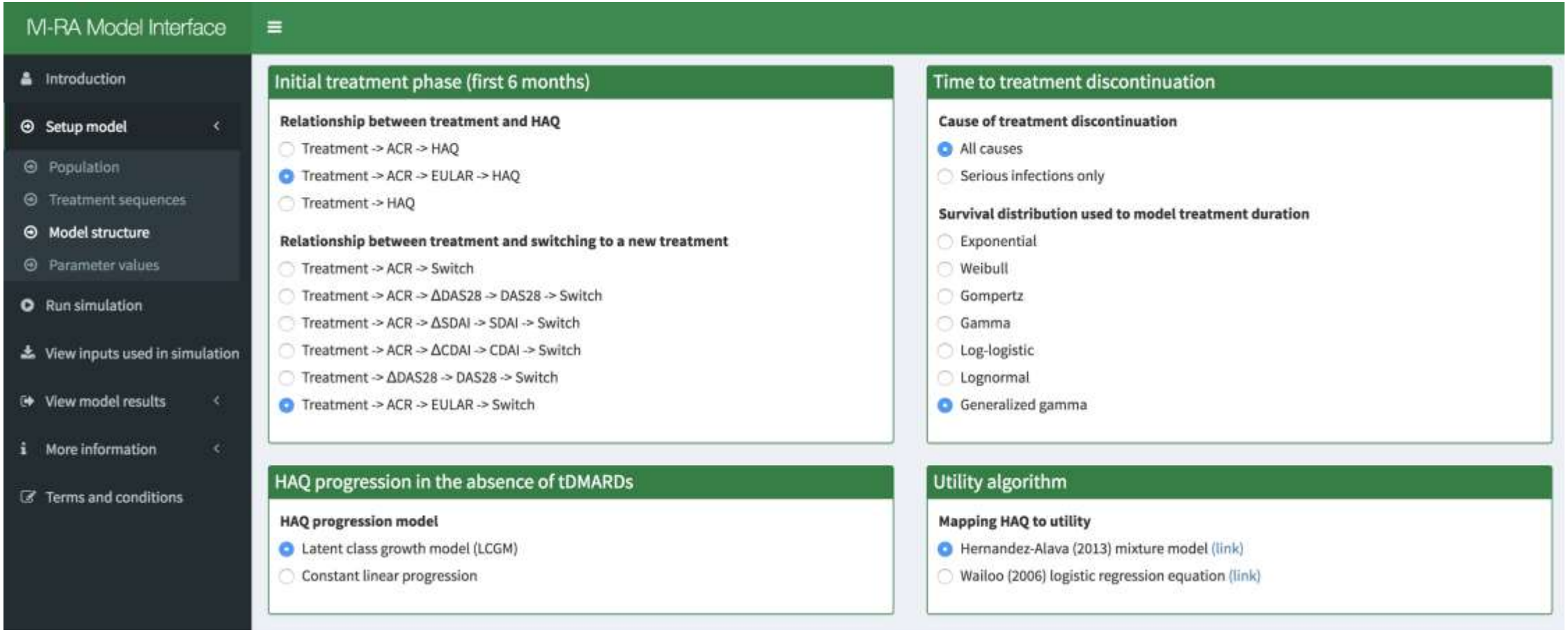
IVI-RA package GitHub directory structure

- **data-raw**: Raw data and all statistical analysis scripts to produce model inputs (reproducible via a Makefile)
- **data:** Model inputs created using scripts in data-raw
- **docs**: Model documentation including package website and PDF technical document
- **R**: Code for functions needed to run the model with R
- **src**: C++ code for the IPS. Linked to R with *Rcpp*
- **tests:** Hundreds of unit tests via R package *testthat* to help ensure the code works as intended



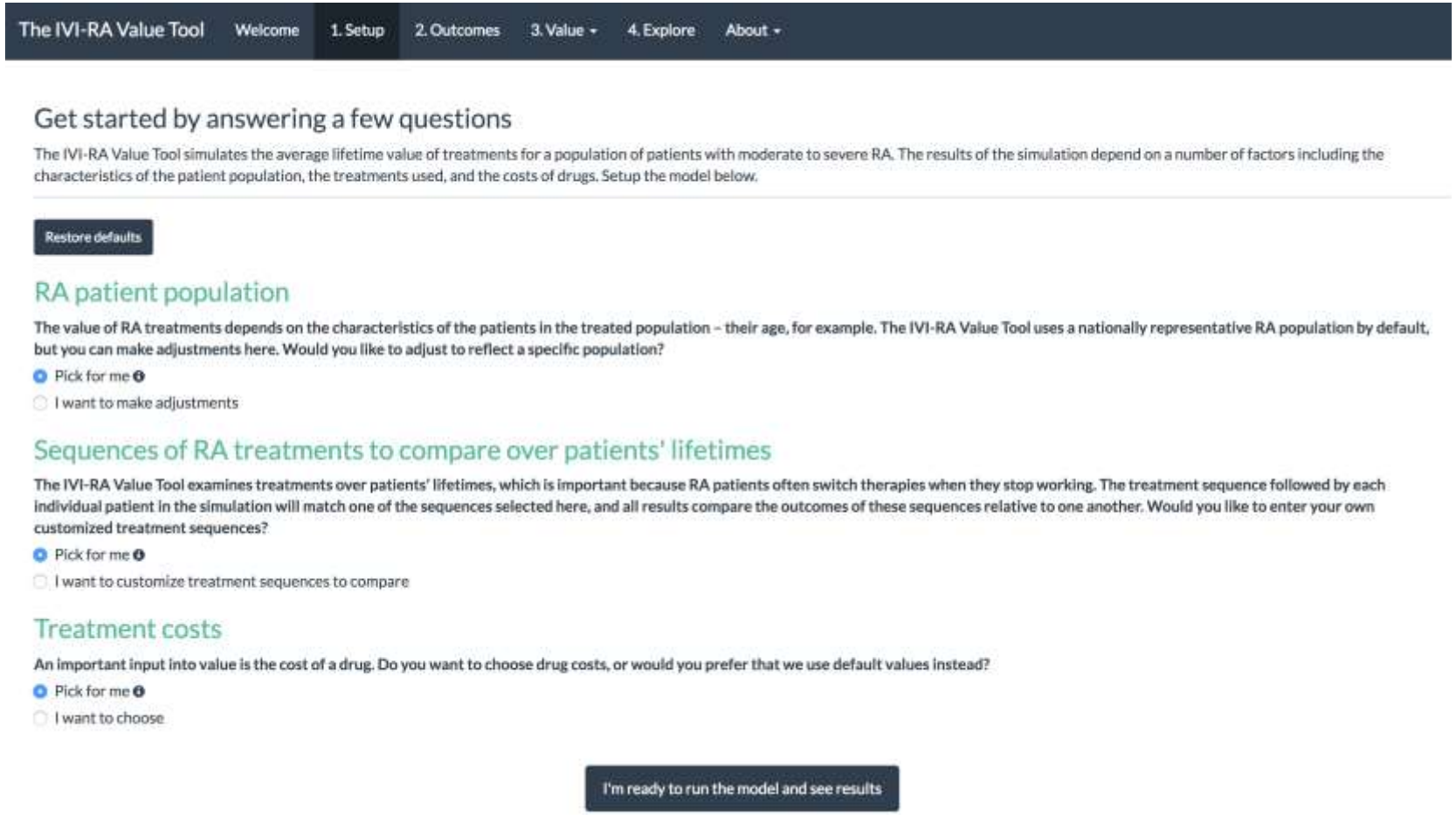
IVI-RA model interface

- Run custom analyses without any knowledge of R (or C++)
- Pressure test the model



IVI-RA value tool

- An important aim of OSVP is to obtain feedback from as many relevant stakeholders as possible
- A general audience web-application allowing those who are not experts in modeling or health economics to interact with the model



Conclusion

- The IVI-RA model is developed as part of the OSVP designed to overcome the limitations of traditional approaches to model-based value assessment in the context of the US decentralized decision-making environment.
  - limited transparency, lack of flexibility to perform analyses representative of the local setting, difficult to update, and insufficient quantification of uncertainty.
- The IVI-RA model is an open-source script-based (R and C++ software) model with different web-interfaces to allow technical and non-technical users to interact with the model.
- It enables a more constructive dialogue between different stakeholders with different beliefs about relevant clinical data, modeling approaches, and value perspectives.
- The model facilitates iterative development and collaboration between multiple clinical and methodological experts with the ultimate aim of having a transparent model useful and acceptable for many stakeholders.

Thank you

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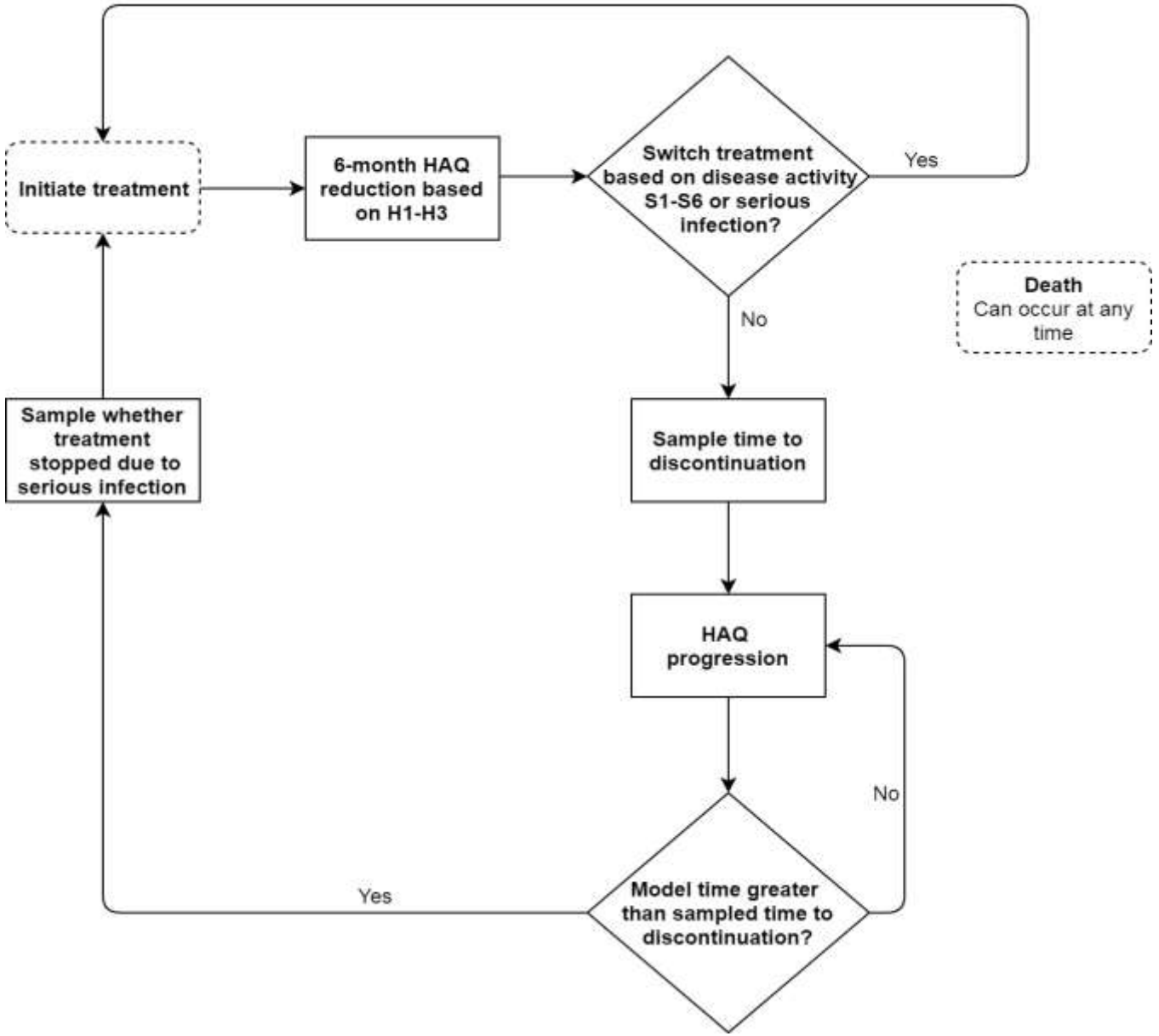
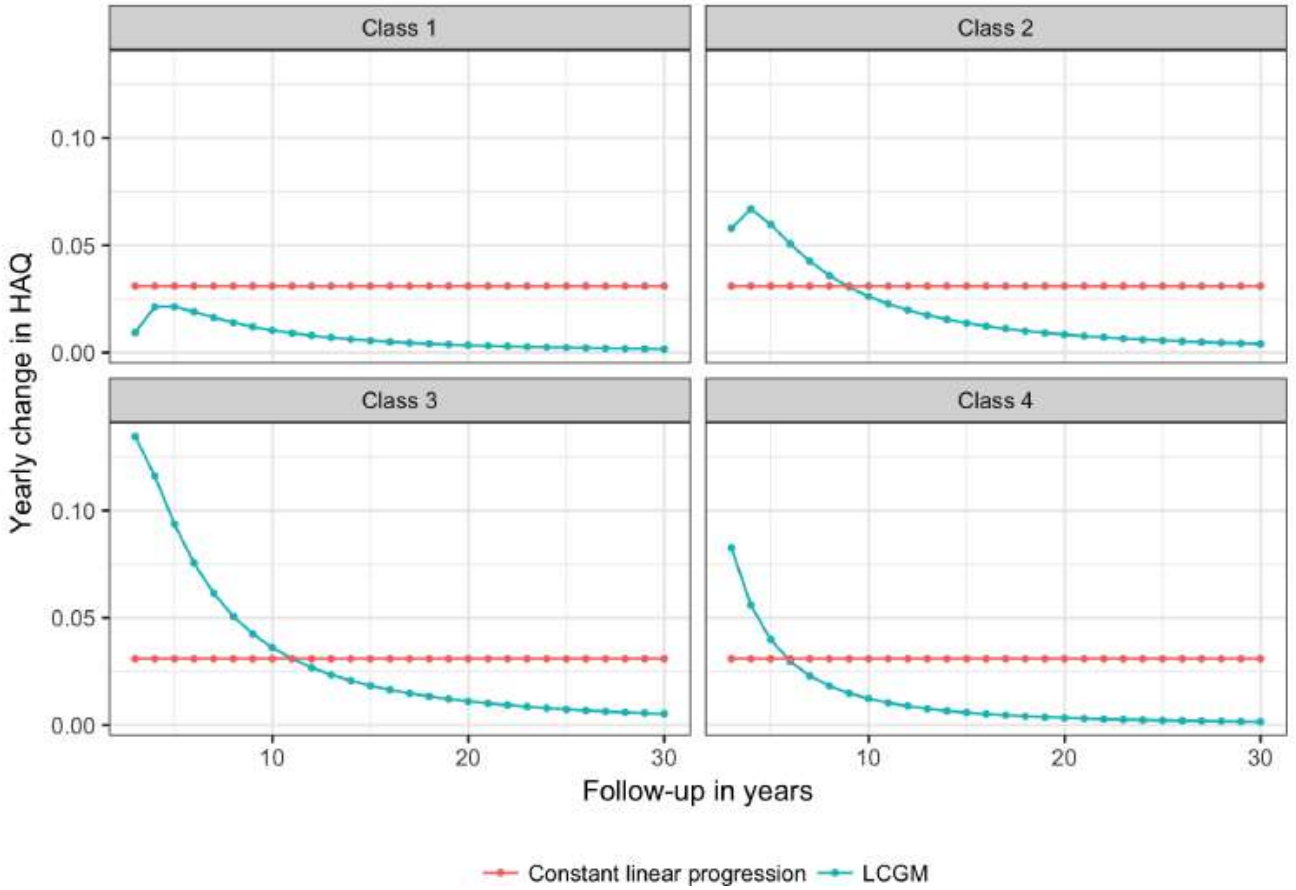
BACK-UP

Flow diagram of the simulation of a single patient



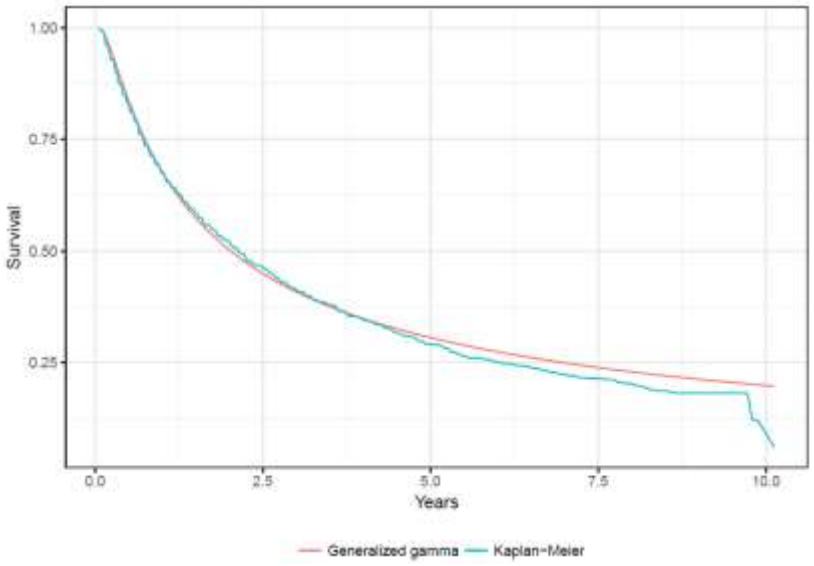
Long term progression of HAQ

- Constant rate of progression
- Latent class growth model
  - Different subgroups have distinct HAQ trajectories and the rate of worsening of HAQ progression decreases over time

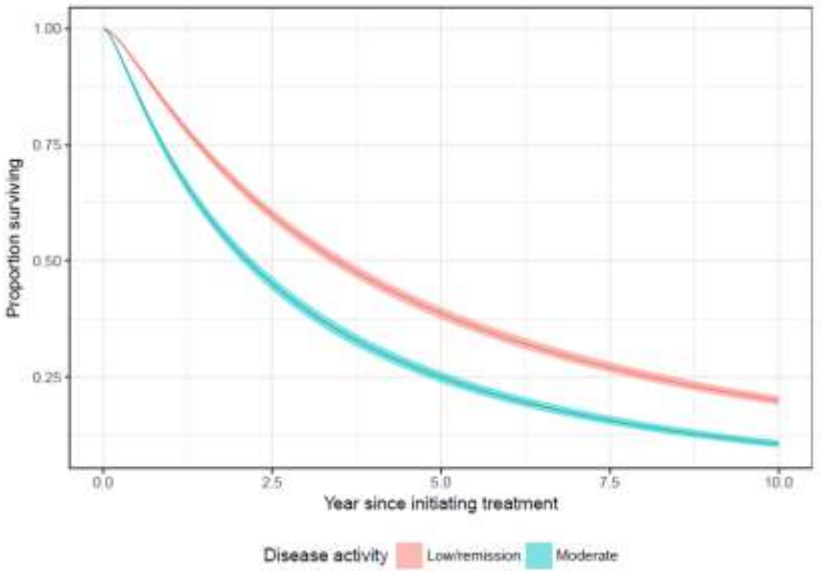


Duration of maintenance treatment

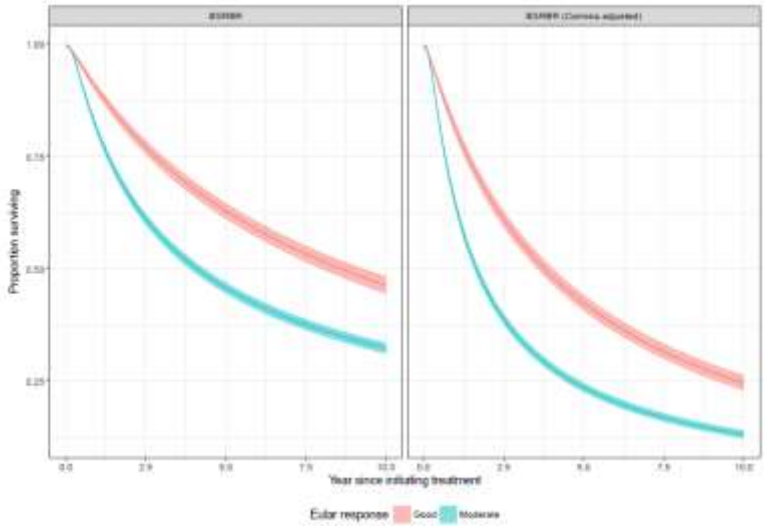
Non-stratified



By disease activity level

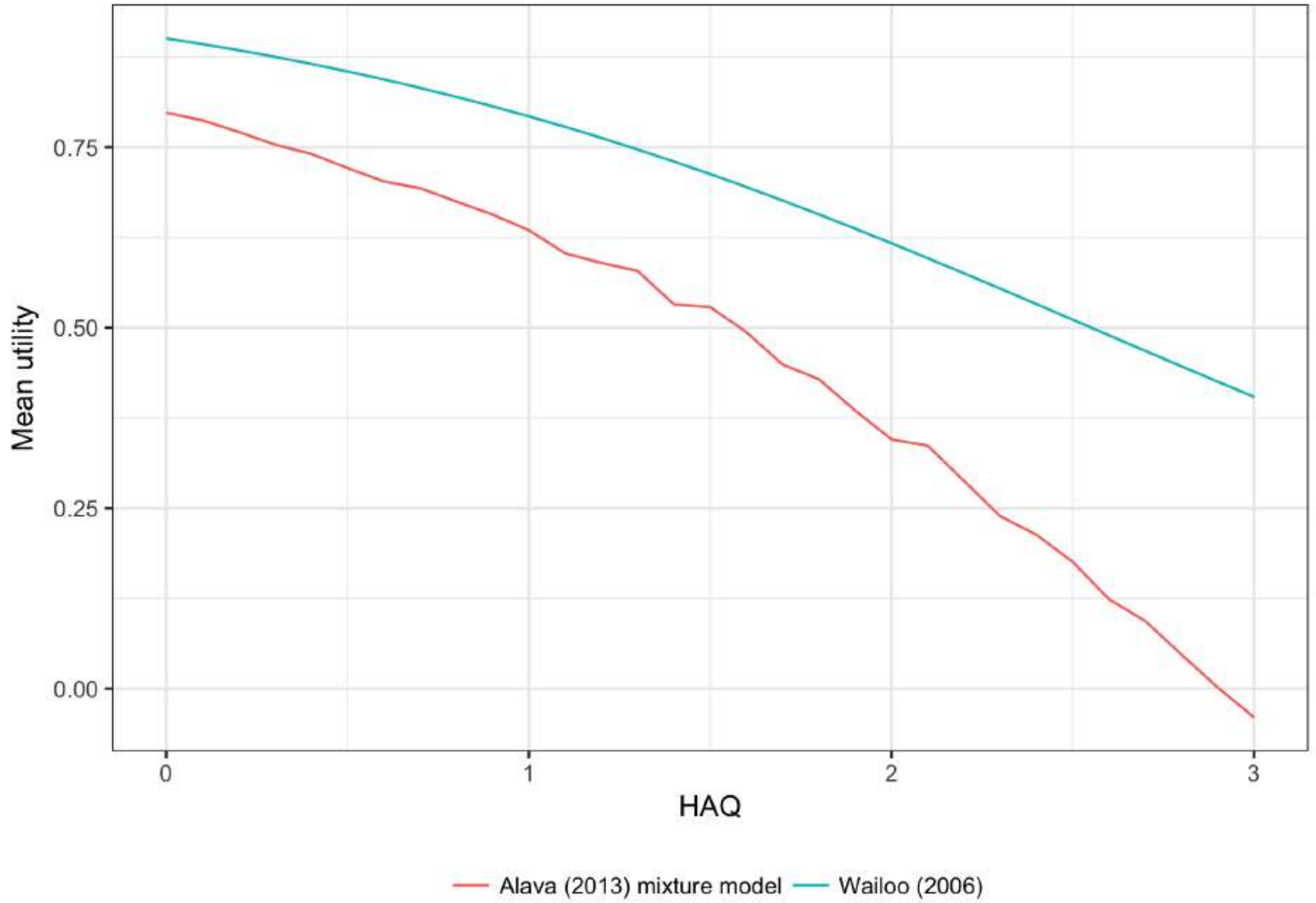


By EULAR response



7 possible parametric distributions: exponential, Weibull, Gompertz, gamma, lognormal, log-logistic, and generalized gamma

Utility


Mean utility
0.75
0.50
0.25
0.00
0
1
2
3
HAQ
Alava (2013) mixture model
Wailoo (2006)

Areas for improvement

- Clinical
  - Trends in disease activity (DAS28/SDAI/CDAI) over time
  - Correlation between disease activity and HAQ
  - Other adverse events
  - Treatment effect modifiers
  - HAQ rebound
  - Treatment effect after failing a targeted DMARD
- Model validation
- Model averaging
- Individualized value assessment

IVI-RA R package tutorial

IVI-RA Tutorial API Collaborate About Web apps

Sampling the model parameters

The `iviRA` package does not allow users to run the IPS with parameters set to fixed values, but instead recognizes that parameter values are inherently uncertain. As such, all parameters are randomly sampled from their (joint) probability distribution and the IPS is run for each randomly sampled parameter set. The parameters are sampled using the function `sample_pars`, which generates a probability distribution for all model parameters.

The random samples depend on the underlying statistical estimates of the distribution of the parameters. We can generate a sample of size 100 using default values.

```
parsamp <- sample_pars(n = 100, input_data = input.dat)
```

The object `parsamp` returned from `sample_pars` is a list of random draws of the parameters used in the IPS.

```
names(parsamp)
```

```
##  [1] "n"                "acr"              "das28"
##  [4] "haq"              "acr2haq"          "acr2das28"
##  [7] "acr2sdai"         "acr2cdai"         "acr2eular"
## [10] "eular2haq"        "rebound"          "haq.lprog.tx"
## [13] "haq.lprog.age"    "haq.lcgm"         "lt"
## [16] "mort.logor"       "mort.loghr.haqdif" "ttd.all"
## [19] "ttd.da"           "ttd.eular"        "ttsi"
## [22] "tx.cost"          "hosp.cost"        "mgmt.cost"
## [25] "si.cost"          "utility.mixture"  "utility.wailoo"
## [28] "si.ul"            "utility.tx.attr"  "prod.loss"
```

Contents

Unit testing

The IVI-RA package contains hundreds of unit tests to help ensure that the code works as intended

Each time the code is pushed (e.g., updated) to GitHub:

- It is re-compiled and installed on an external Ubuntu machine with Travis-CI
- codecov.io estimates the percent of the code that is covered by the tests

```
test_that("rsurvC", {
  n <- 10

  ## exponential distribution
  fit <- flexsurv::flexsurvreg(Surv(futime, fustat) ~ age, data = ovarian,
                               dist = "exp")
  fit.lrate <- fit$coef %*% x
  set.seed(50)
  samp1 <- rexp(n, rate = exp(fit.lrate))
  set.seed(50)
  samp2 <- replicate(n, iviRA:::rsurvC(fit.lrate, anc1 = 0, dist = "exponential"))
  expect_equal(samp1, samp2)
```