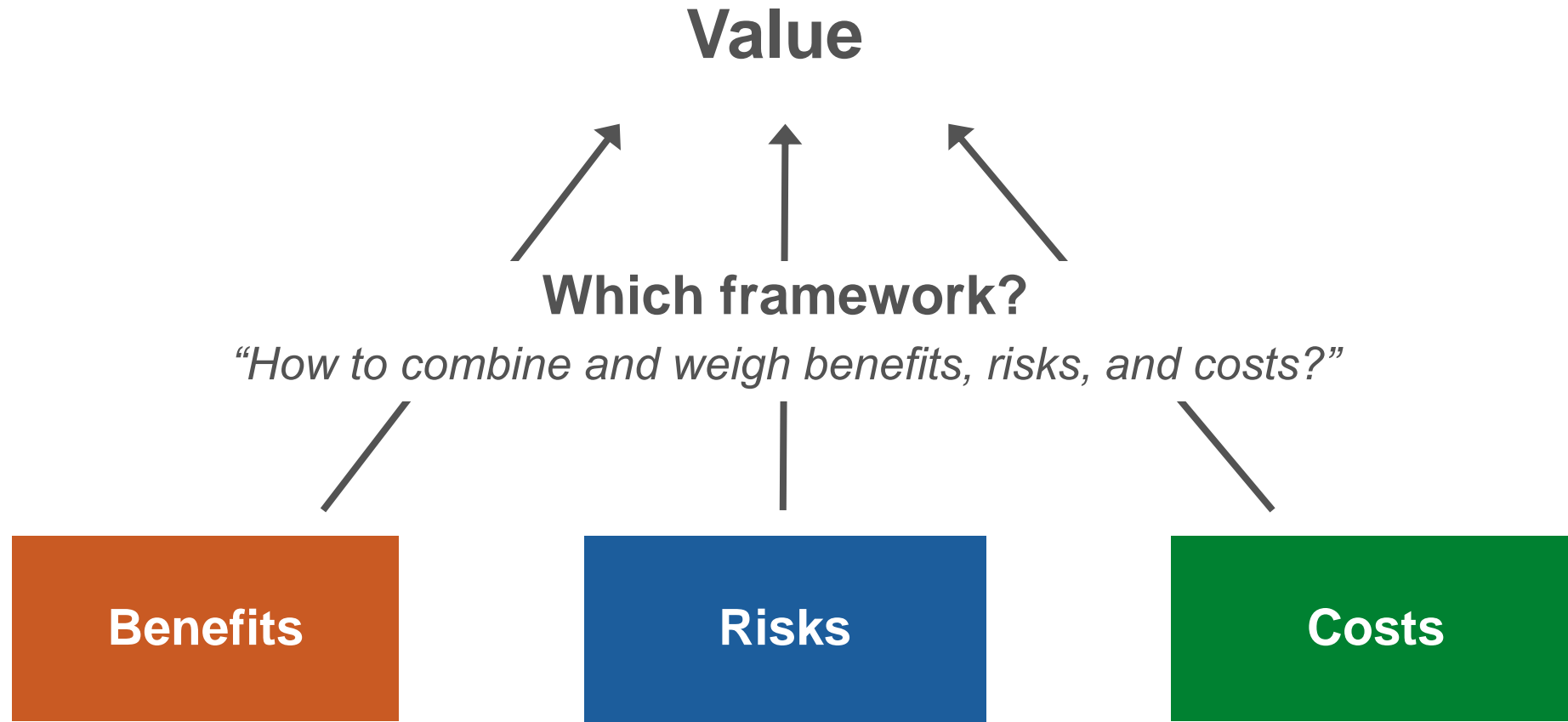


An open-source cost-effectiveness simulation model for rheumatoid arthritis in R

Jeroen P Jansen PhD

Value assessment? Yes, but how?



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

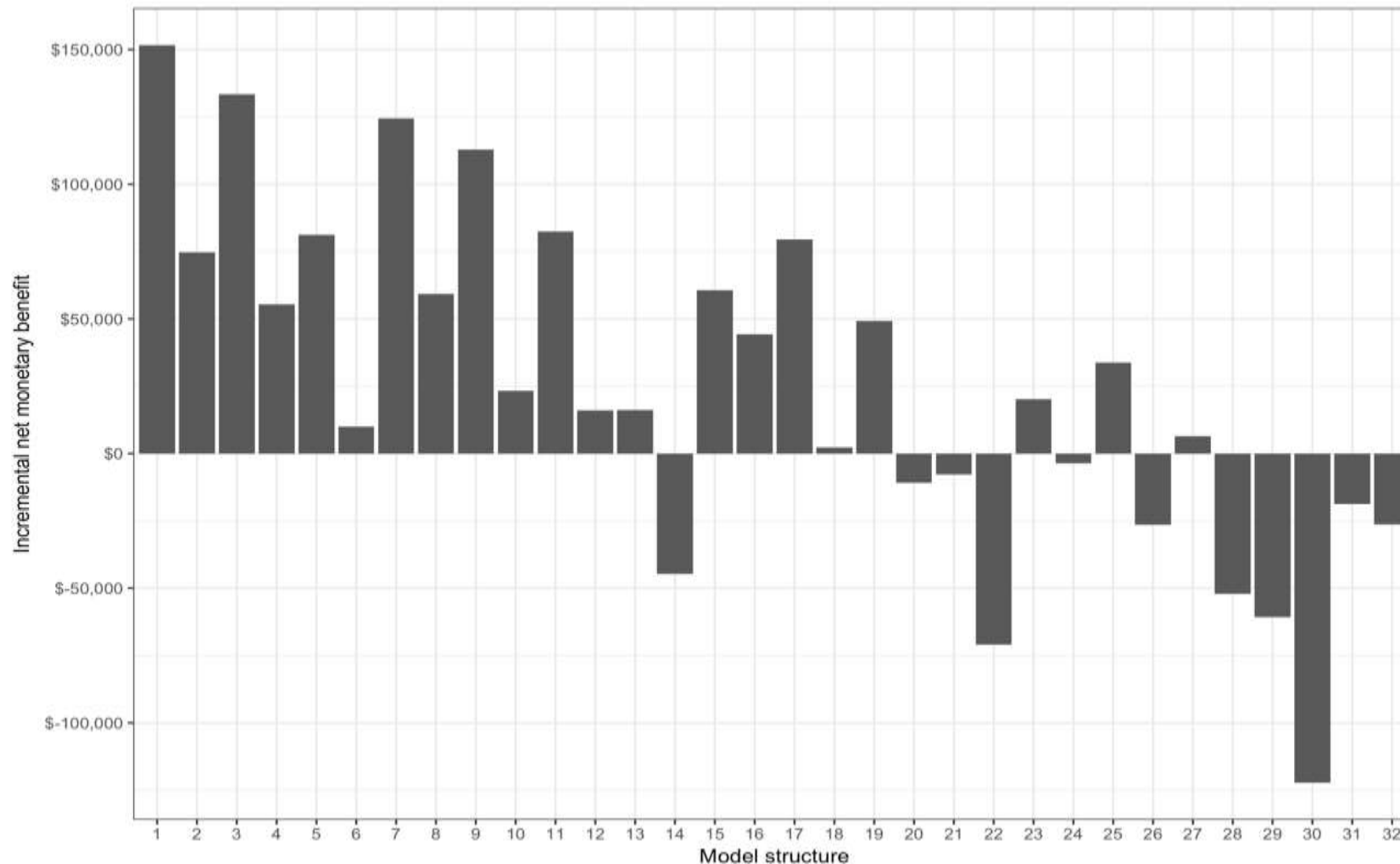
Credibility and Relevance of published model-based assessments of value?

- > 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 Quickly outdated given pace of new clinical evidence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

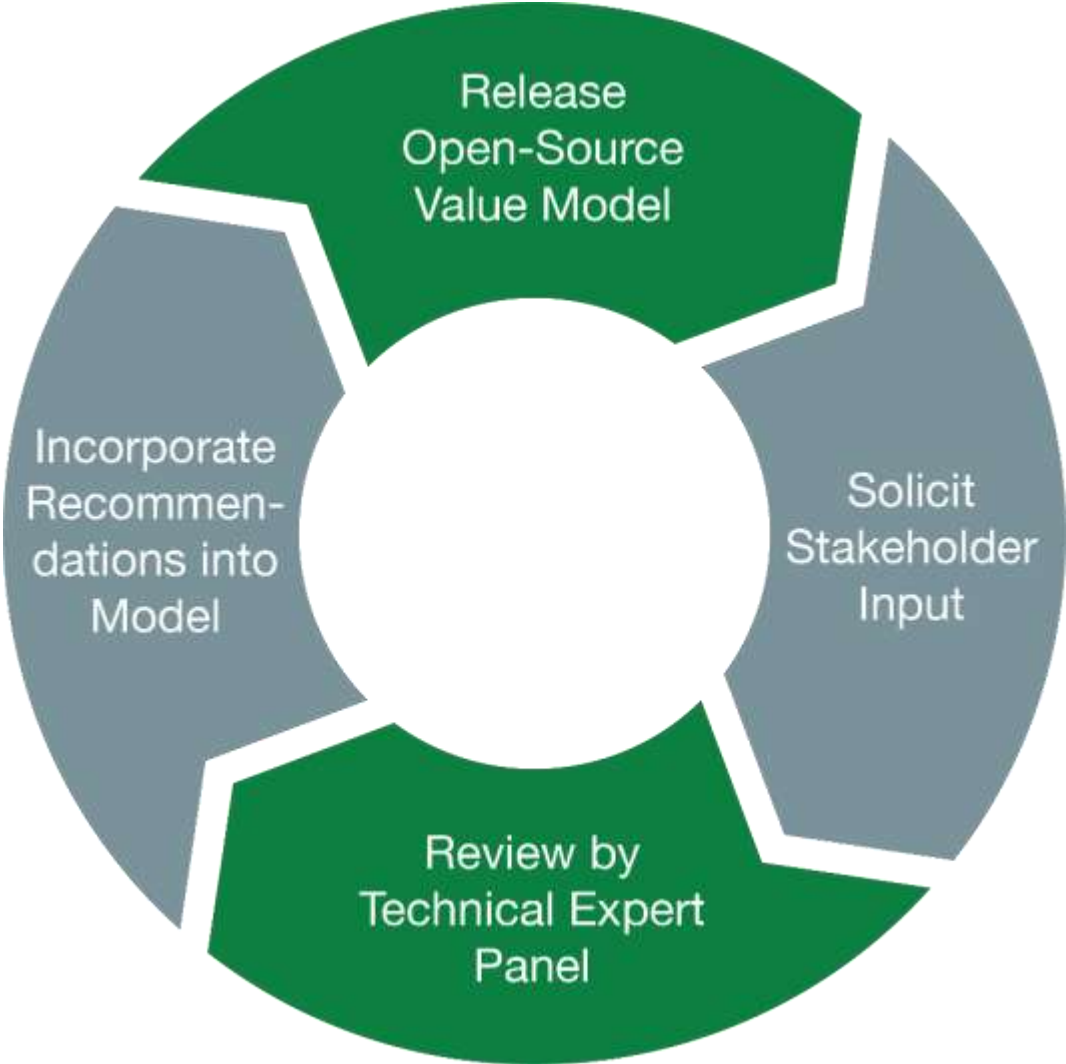
Sensitivity of findings to 32 competing structural assumptions in IVI-RA model. Incremental net-monetary benefit (at WTP of 150,000 US\$) with sequential targeted DMARD treatment relative to conventional DMARD treatment



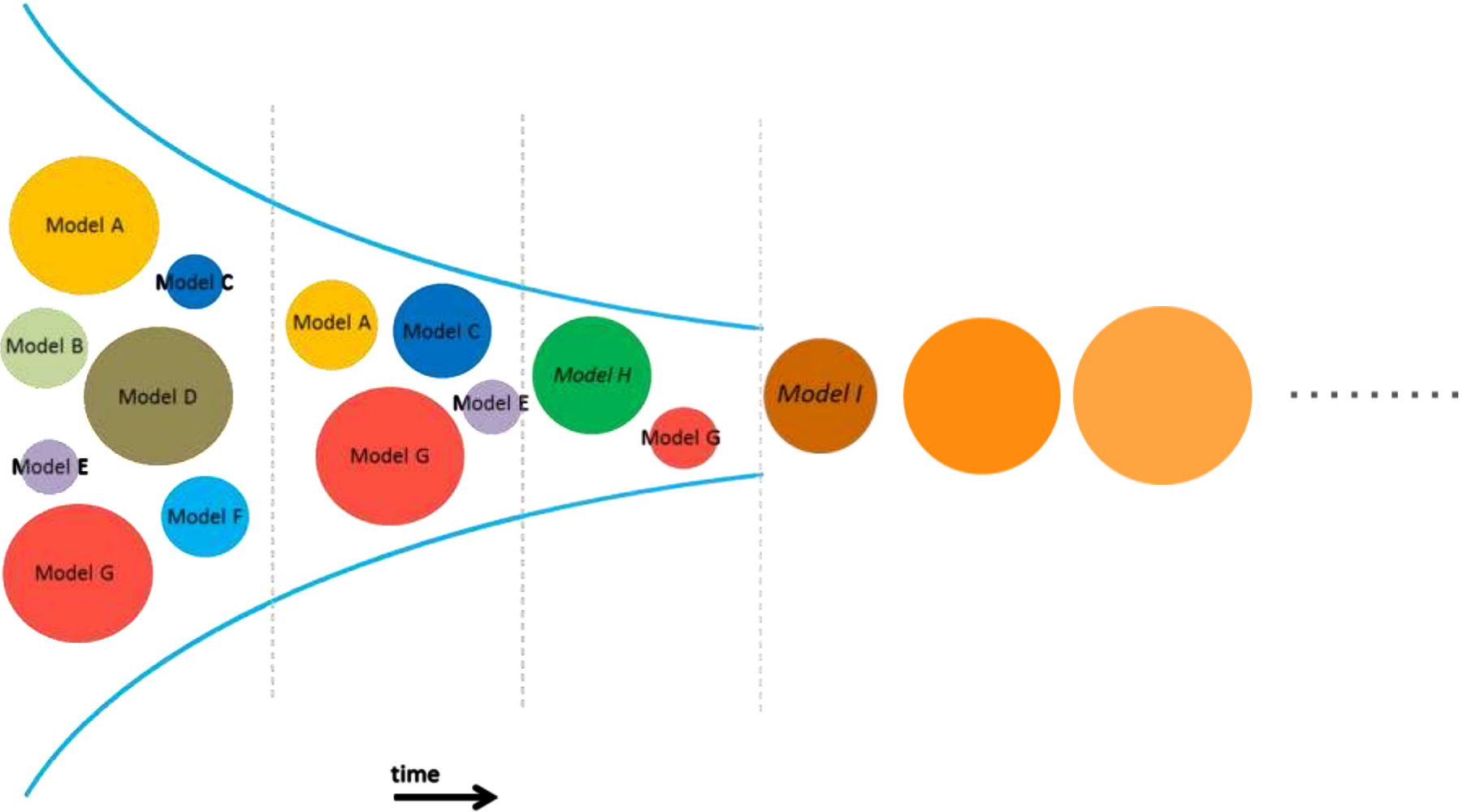
Open Source Value Project (OSVP)

- > 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



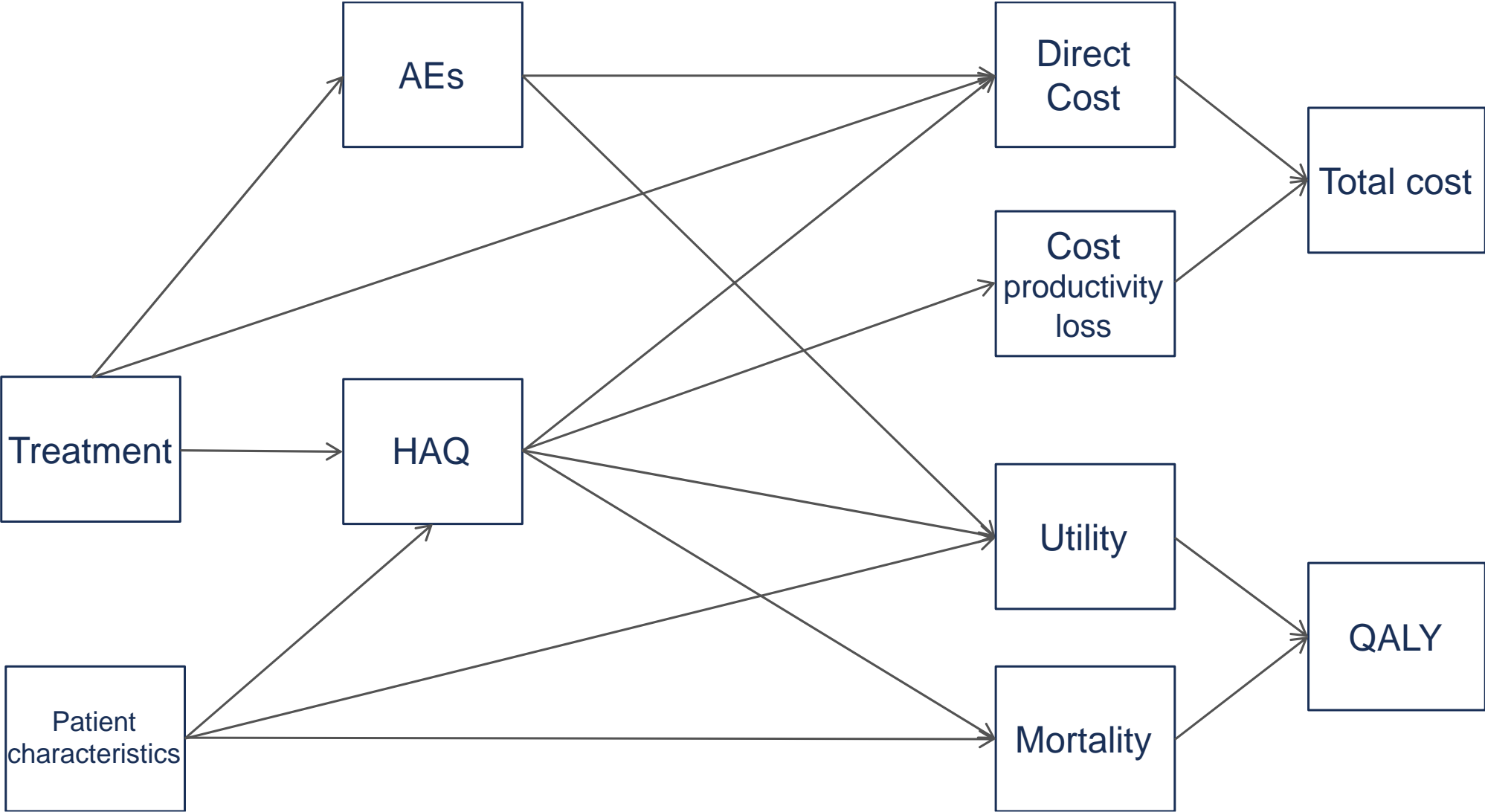
Crowd-sourcing expertise & model averaging



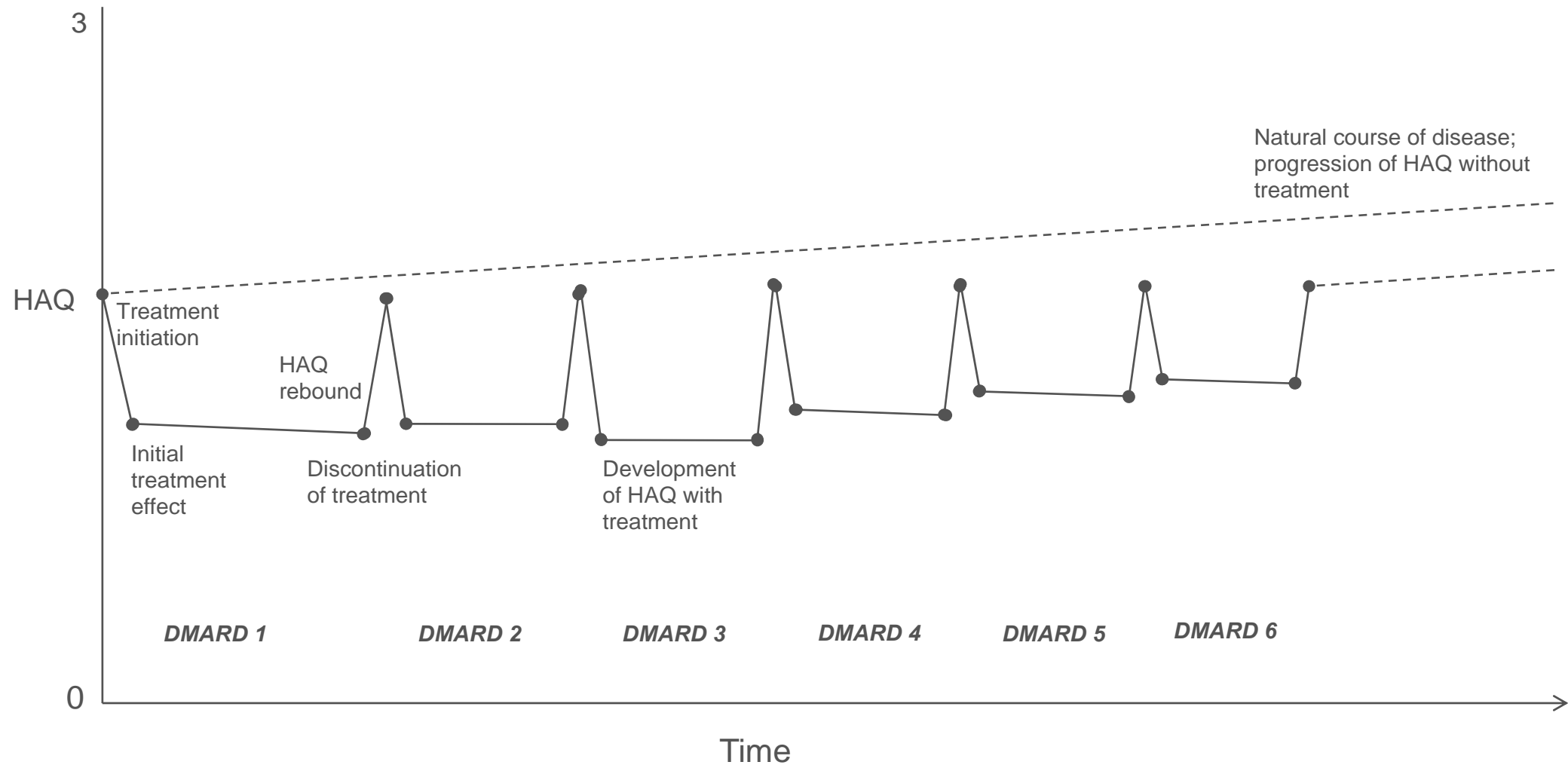
IVI-RA model

- > 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

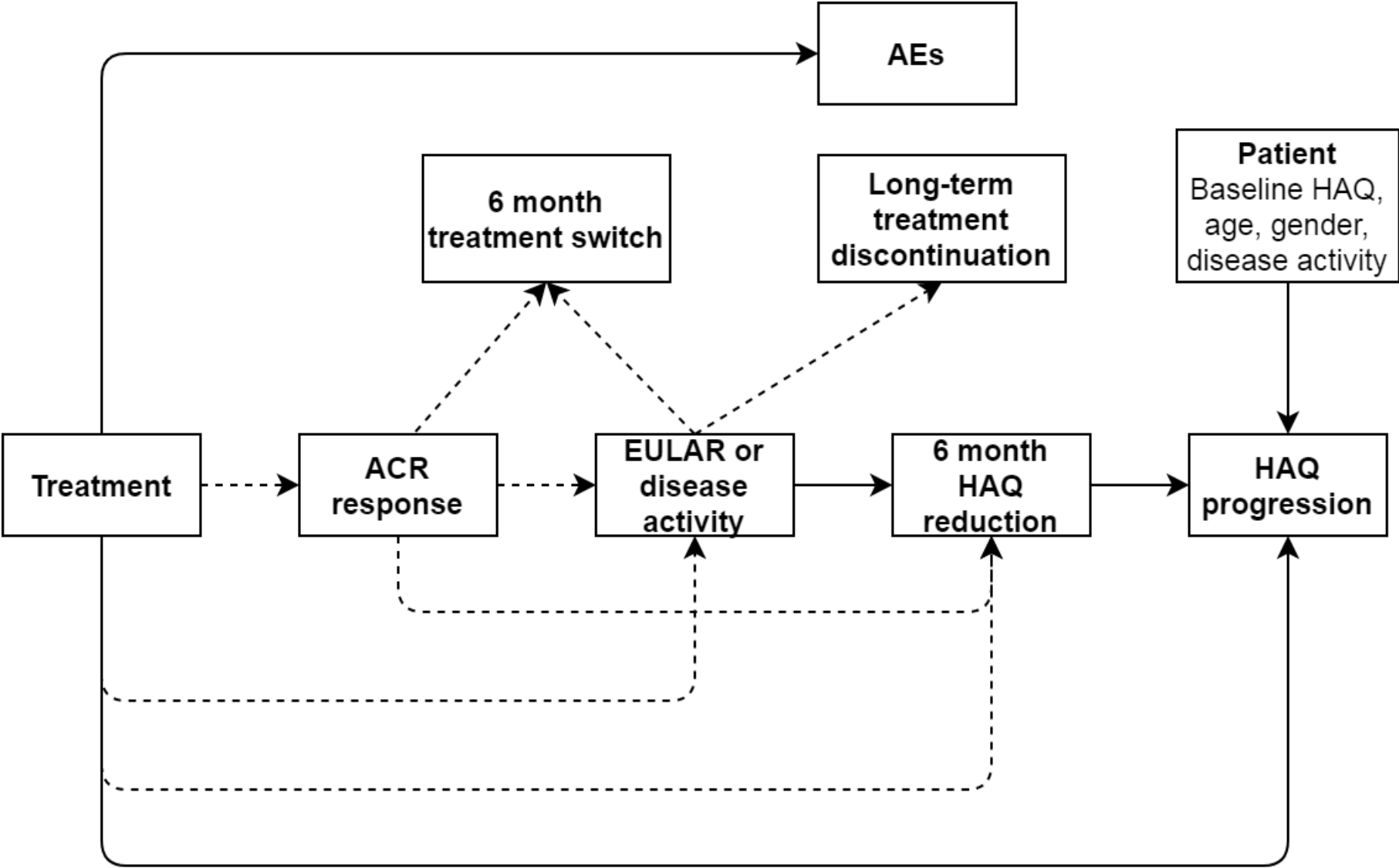


Competing model structures

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		<ul style="list-style-type: none"> • US life tables • Impact of HAQ on mortality 	
Resource use		<ul style="list-style-type: none"> • 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



IVI-RA Value Tool



IVI-RA Model Interface



IVI-RA R-package



R and C++ source code (GitHub)

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("lcm", "linear"),
                                       ttd_cause = c("all", "si"),
                                       ttd_dist = c("gengamma", "exponential"),
                                       utility_model = c("mixture", "wailoo"))

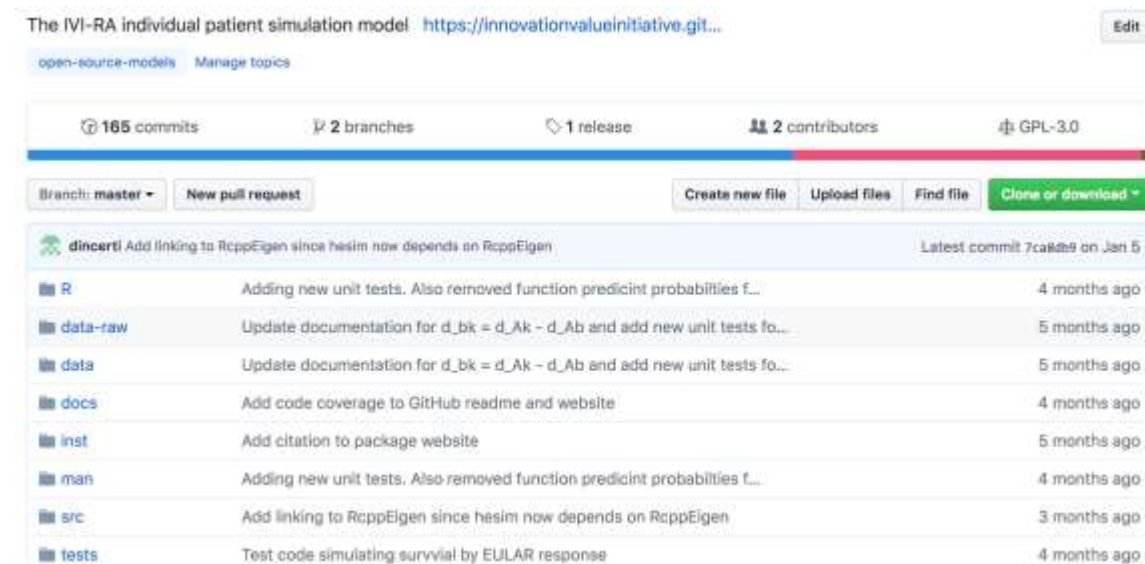
input.dat <- get_input_data(pop = pop)
parsamp <- sample_pars(n = 10, input_dat = input.dat)
sim.out <- sim_ivIRA(tx_seqs = tx.seq, input_data = input.dat, pars = parsamp,
                    model_structures = mod.structs, output = "data")

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



The screenshot shows the GitHub repository page for 'The IVI-RA individual patient simulation model'. The repository has 165 commits, 2 branches, 1 release, 2 contributors, and is licensed under GPL-3.0. The directory structure is as follows:

Directory	Description	Last Commit
R	Adding new unit tests. Also removed function predicint probabilities f...	4 months ago
data-raw	Update documentation for d_bk = d_Ak - d_Ab and add new unit tests fo...	5 months ago
data	Update documentation for d_bk = d_Ak - d_Ab and add new unit tests fo...	5 months ago
docs	Add code coverage to GitHub readme and website	4 months ago
inst	Add citation to package website	5 months ago
man	Adding new unit tests. Also removed function predicint probabilities f...	4 months ago
src	Add linking to RcppEigen since hesim now depends on RcppEigen	3 months ago
tests	Test code simulating survial by EULAR response	4 months ago

IVI-RA model interface

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

The screenshot displays the 'M-RA Model Interface' with a sidebar on the left and four main configuration panels on the right. The sidebar includes: Introduction, Setup model (selected), Population, Treatment sequences, Model structure, Parameter values, Run simulation, View inputs used in simulation, View model results, More information, and Terms and conditions. The main panels are:

- 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 -> Δ DAS28 -> DAS28 -> Switch
 - Treatment -> ACR -> Δ SDAI -> SDAI -> Switch
 - Treatment -> ACR -> Δ CDAI -> CDAI -> Switch
 - Treatment -> Δ DAS28 -> 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](#))

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

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.

[Restore 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](#)

Conclusion

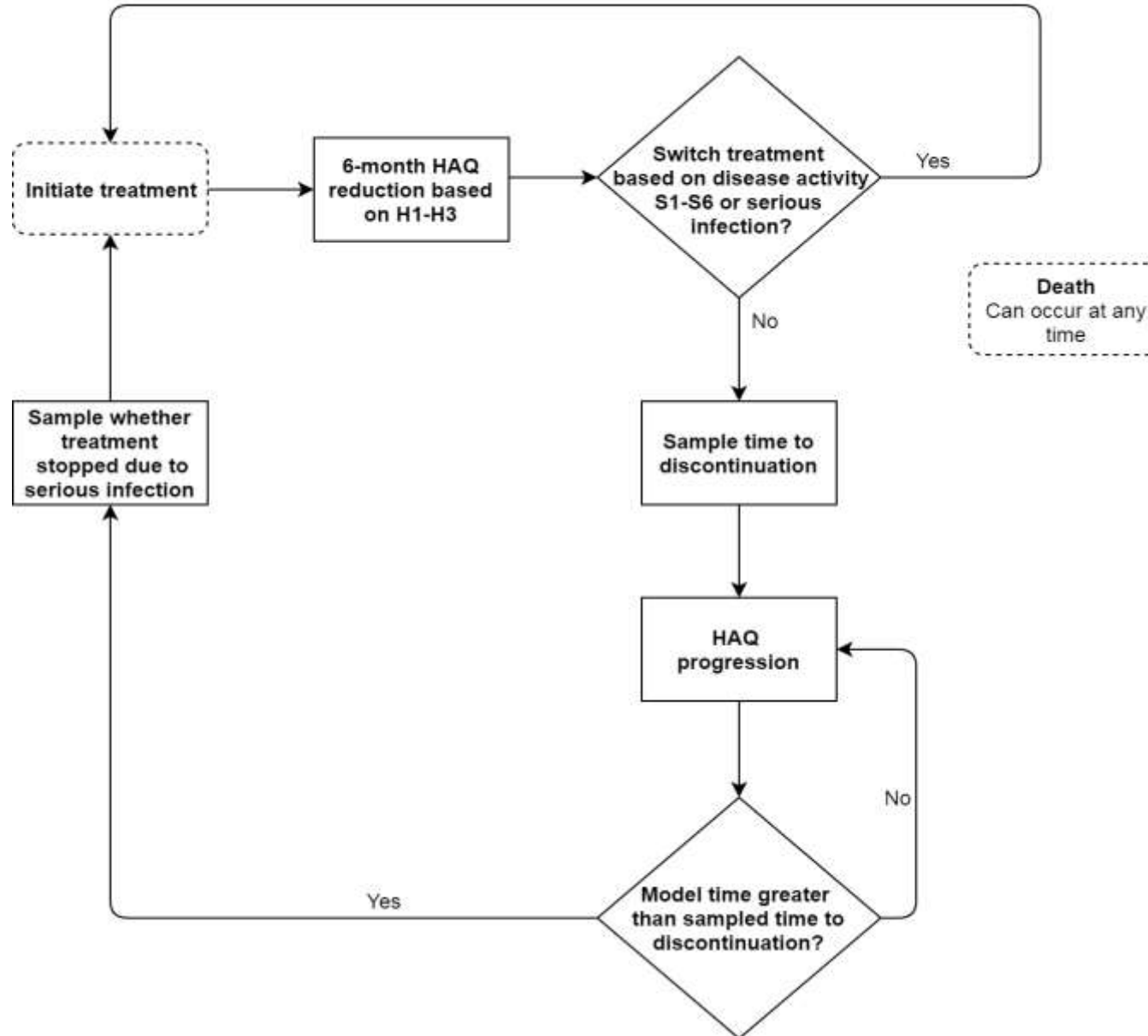
- > The IVI-RA model is developed as part of the OSVP designed to overcome the limitations of traditional approaches to model-based value assessment in the context of the US decentralized decision-making environment.
 - > limited transparency, lack of flexibility to perform analyses representative of 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

jeroen.jansen@thevalueinitiative.org

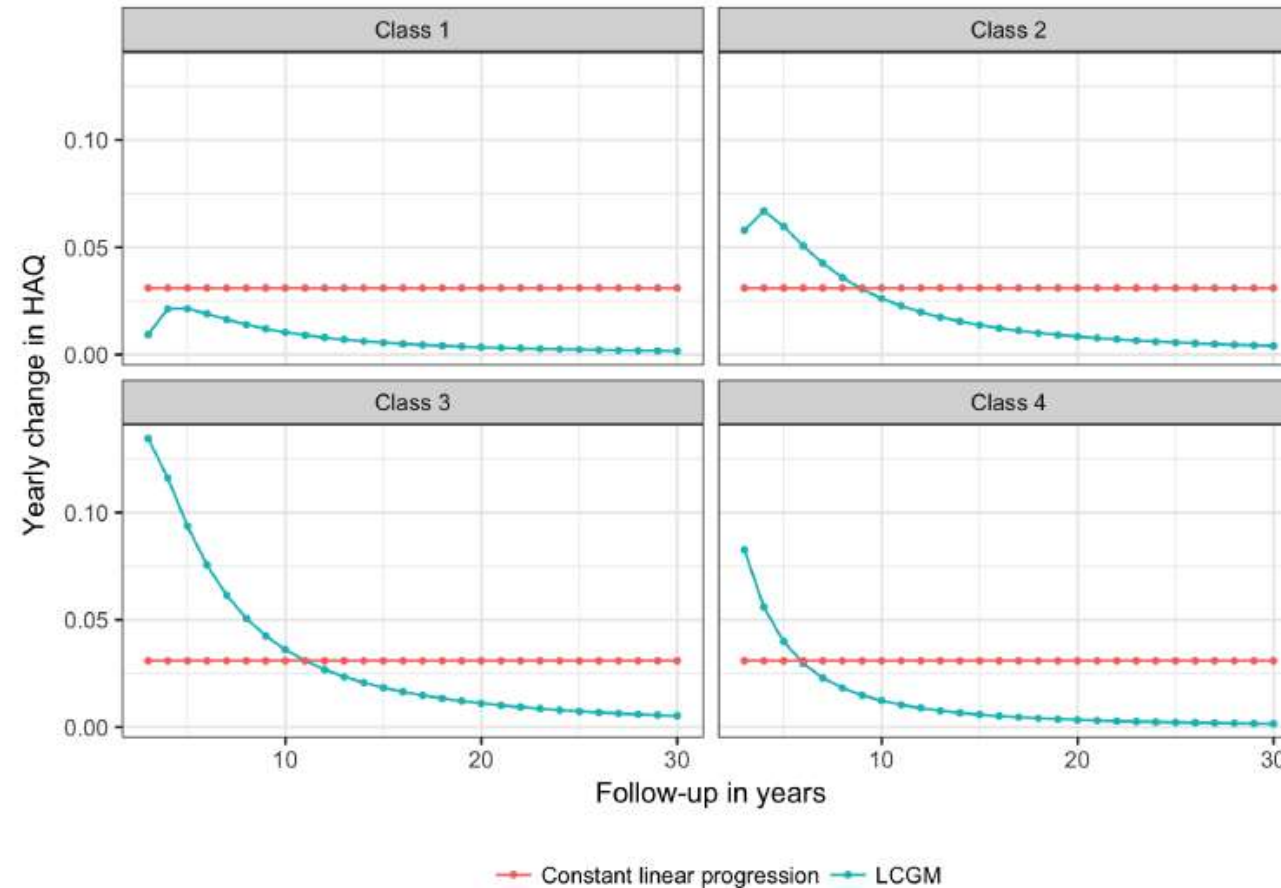
BACK-UP

Flow diagram of the simulation of a single patient



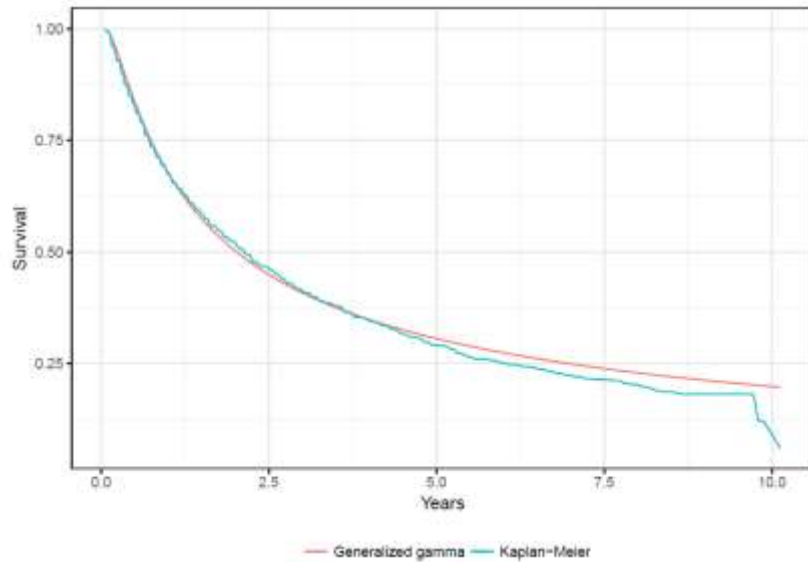
Long term progression of HAQ

- > 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

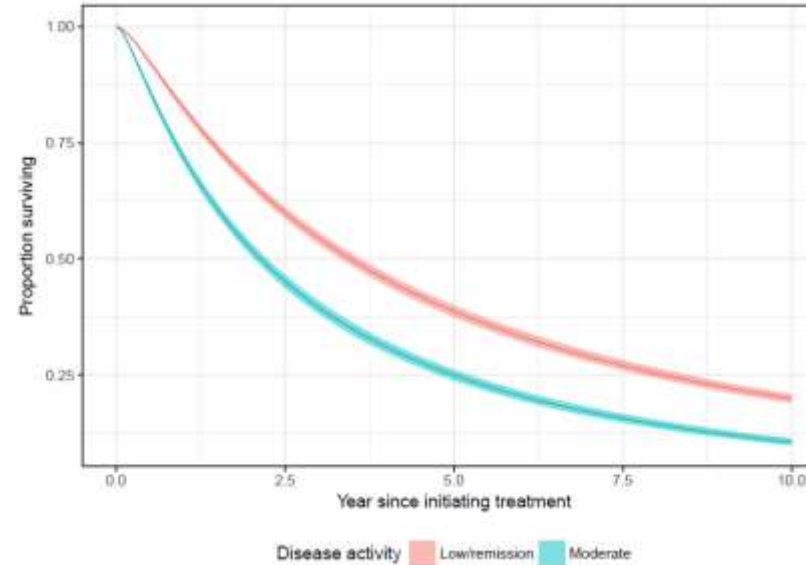


Duration of maintenance treatment

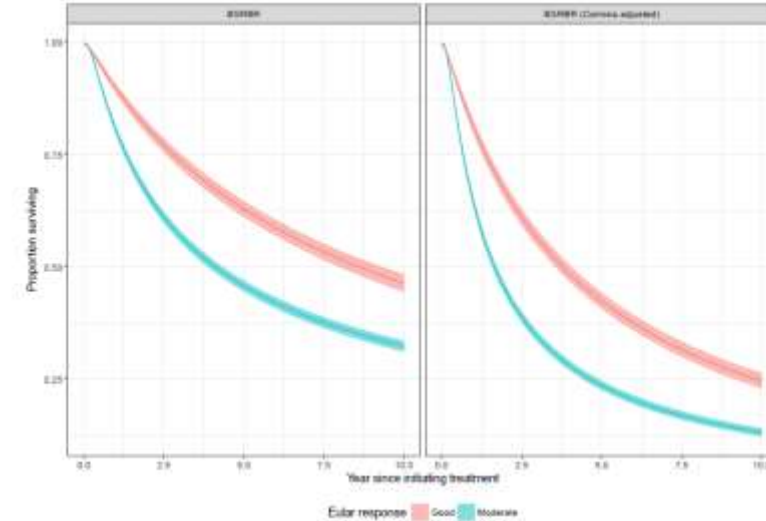
Non-stratified



By disease activity level

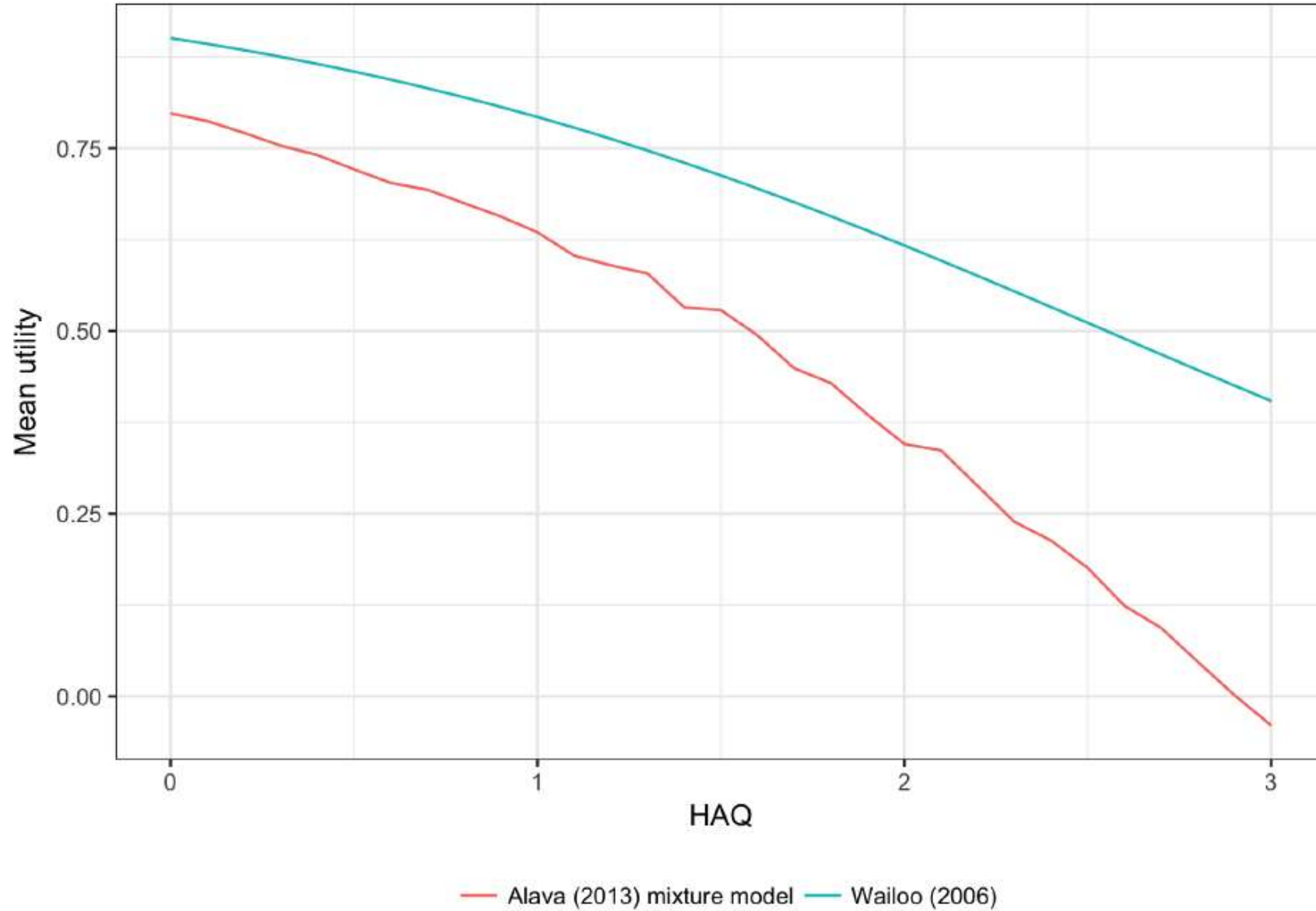


By EULAR response



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

Utility



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



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

[Treatment effects during initial 6 month period](#)

[Treatment response mappings](#)

[Long-term HAQ progression](#)

[Time to treatment discontinuation](#)

[Serious infections](#)

[Mortality](#)

[Utility](#)

[Costs](#)

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)
```

build passing

codecov 91%