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Improving healthcare decisions

Developing flexible, iterative, and transparent decision models

A detailed look at a rheumatoid arthritis individual patient simulation

April 18, 2018

Agenda

- Characteristics of relevant decision models
- Motivating example: the IVI-RA simulation model
- Developing models using R
- Creating web interfaces
- Lessons learned and tools for future model development

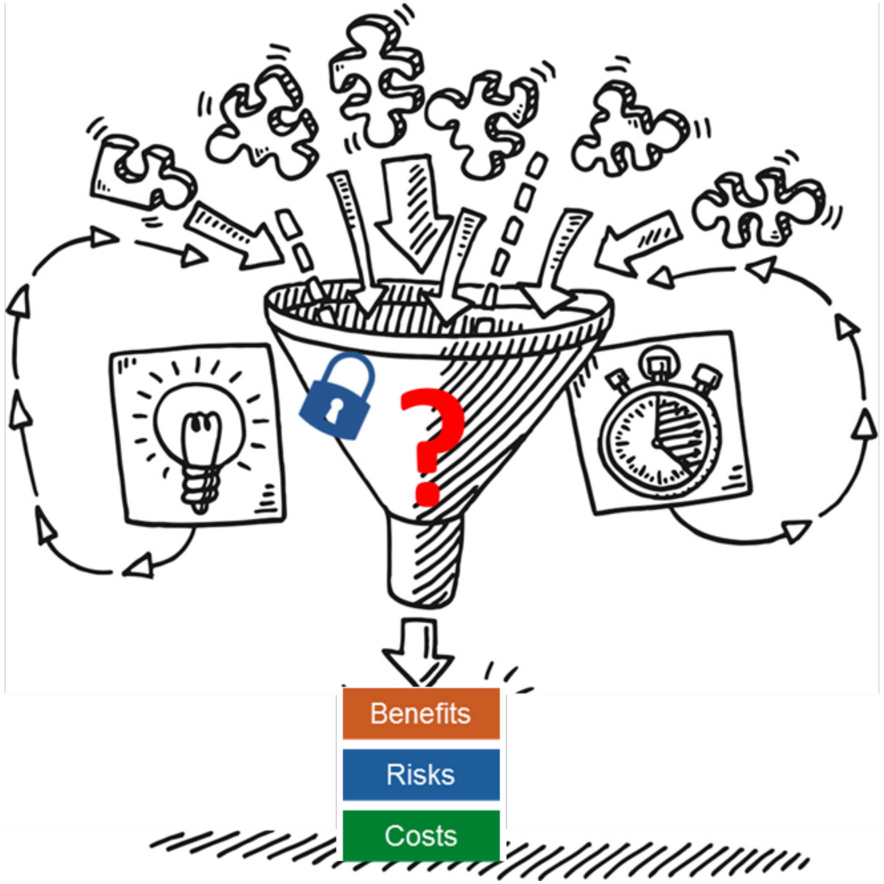
SECTION

1

Characteristics of relevant decision models

Mathematical models play a central role in value assessment

- Frequent need for extrapolations beyond the time-horizon, interventions, outcomes, and settings observed in the available evidence
- Mathematical models are used to combine the findings of different studies to calculate the benefits, risks, and cost of interest for value assessment
- Idiosyncratic choices regarding model structure have an impact on findings
- Lack of transparency
- Cumbersome, if not impossible, for someone other than the original model developer to update the analysis



Barriers to the use of model-based value assessment by decision-makers

- Published model-based CEAs perceived as complex; difficult to judge credibility
- Published CEAs are quickly outdated given pace of new clinical evidence
- Published CEAs may have limited relevance given the local context
- Limited tools to facilitate setting-specific value assessments
- Time constraints

Reducing barriers to decision-making by developing models that are:

- **Flexible:** Tailored to the specific population and disease area of interest, and with sufficient capability for sensitivity/ uncertainty analysis
- **Iterative:** Updated over time as new evidence emerges
- **Transparent:** Easily “pressure tested” by experts and understood by decision-makers

SECTION

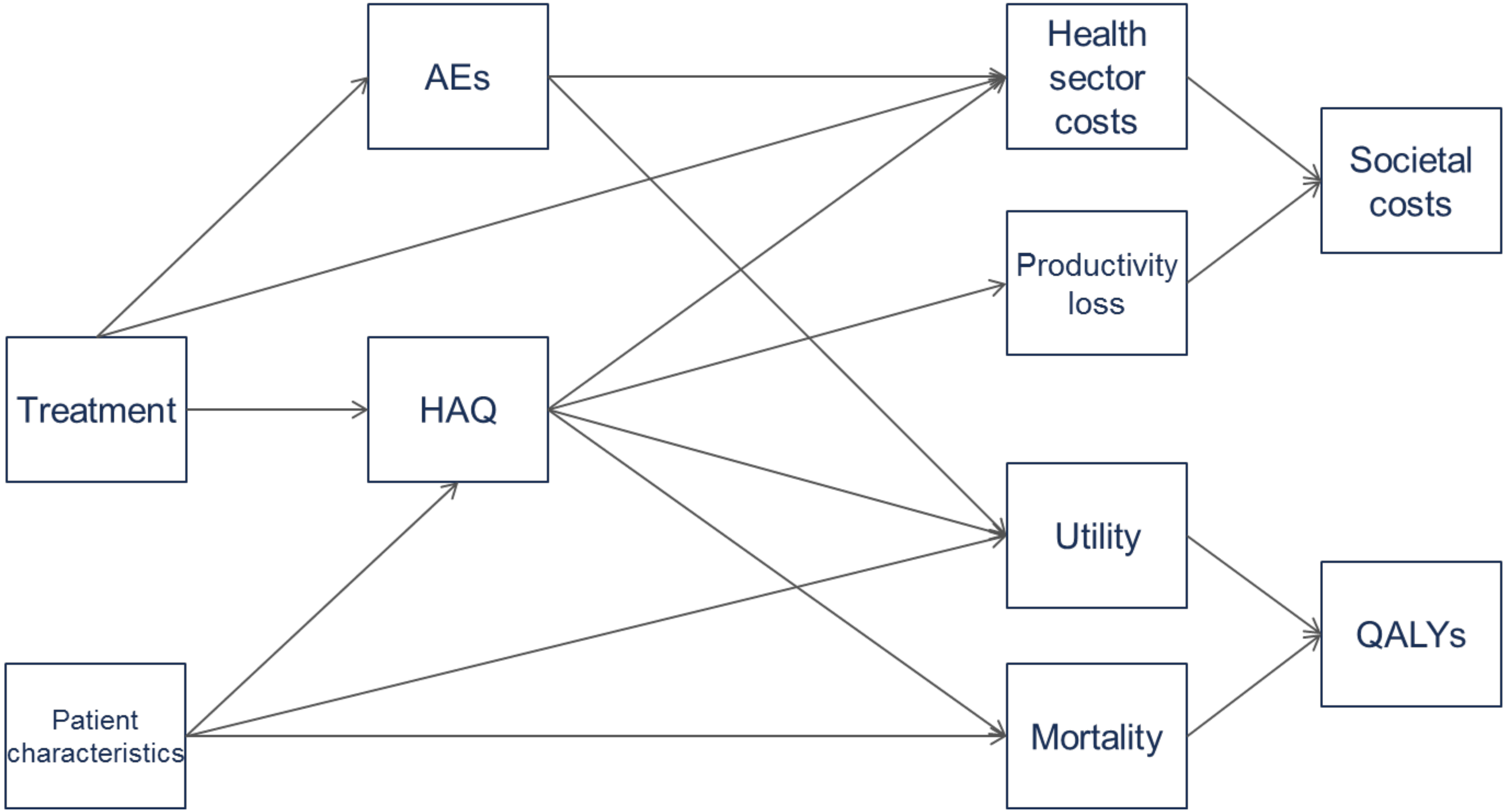
2

Motivating example: the IVI-RA simulation model

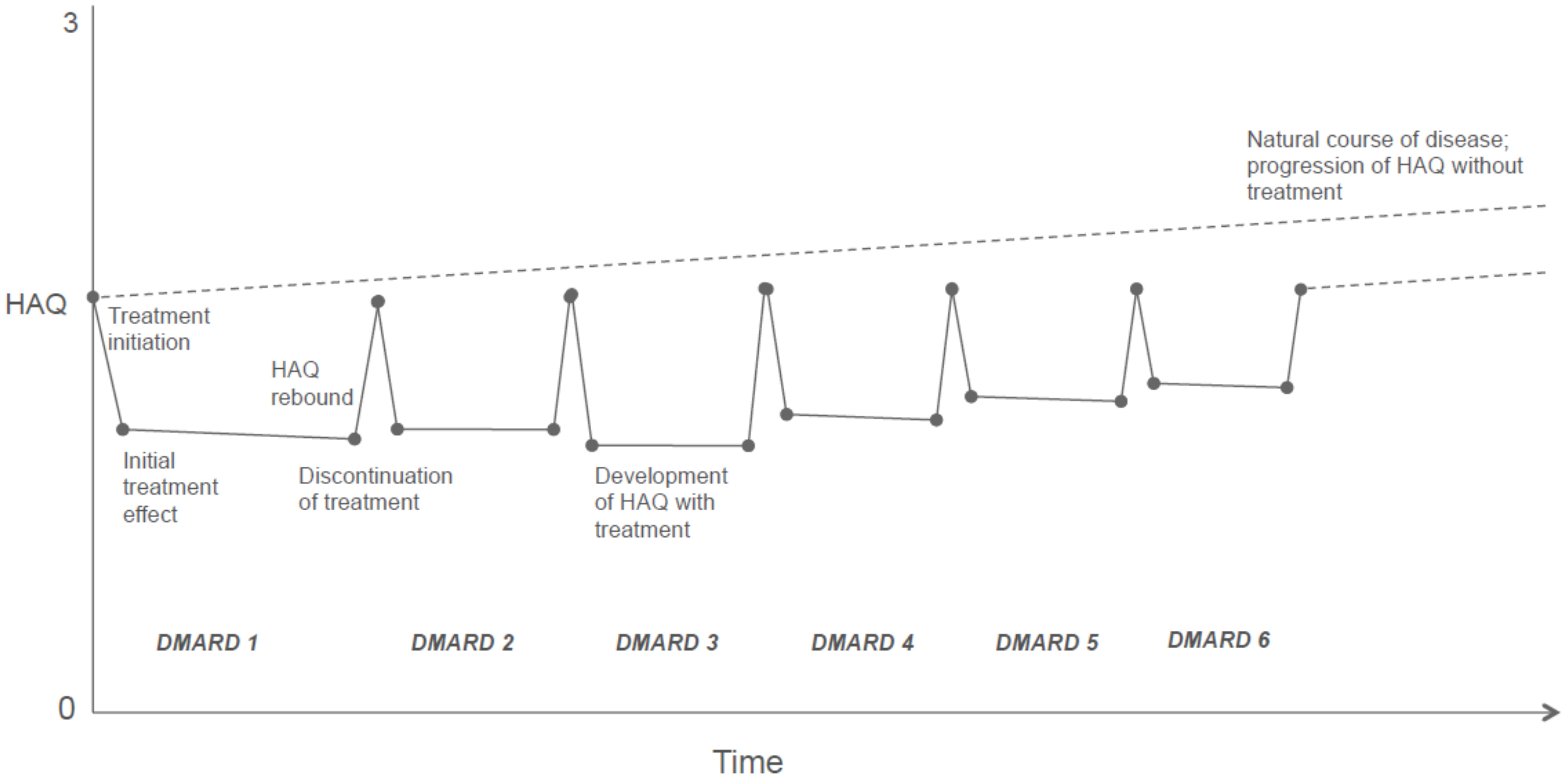
Overview of the IVI-RA model

- 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



Backbone: Development of HAQ over time

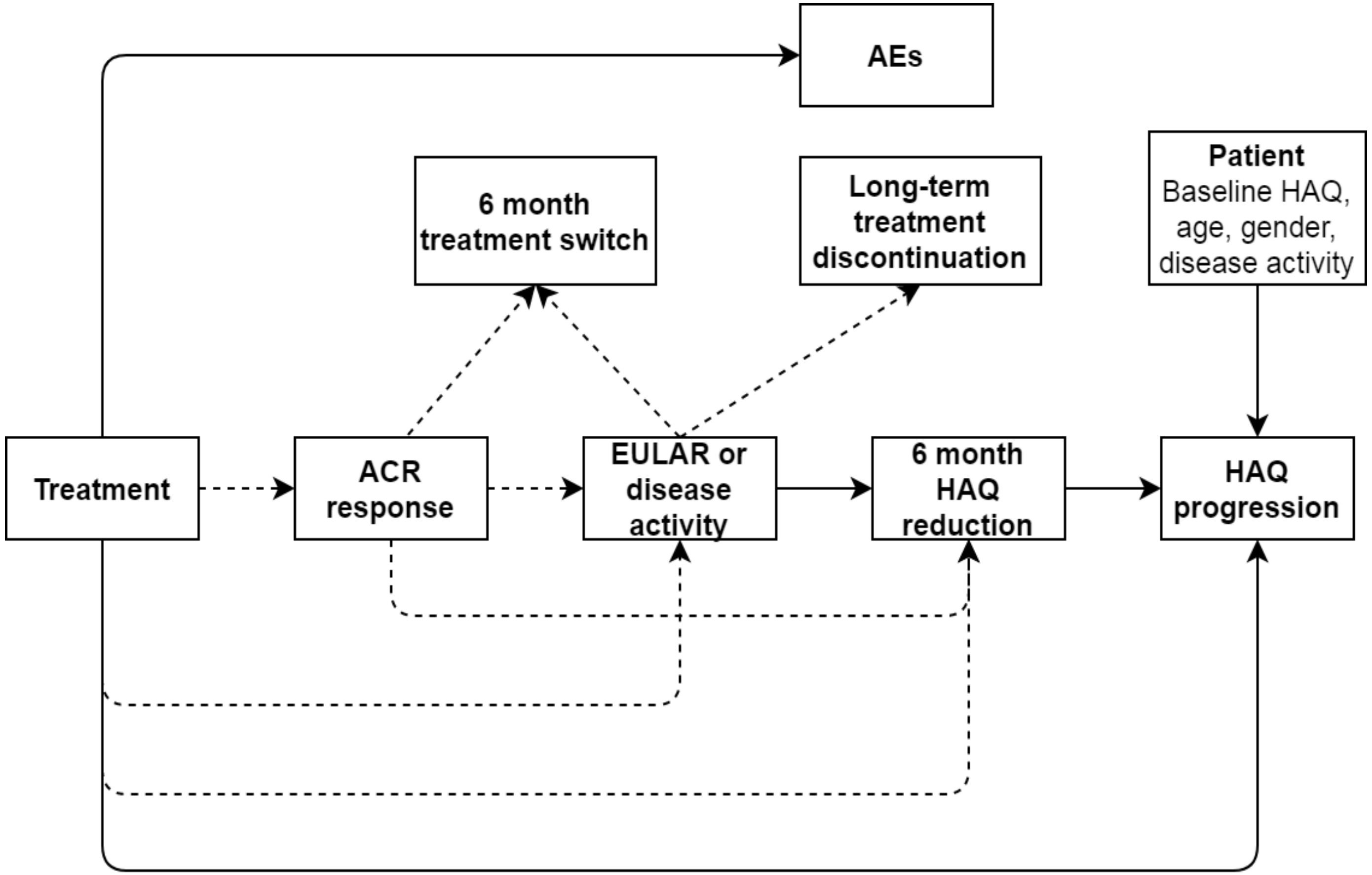


Competing model structures

300+ model structures

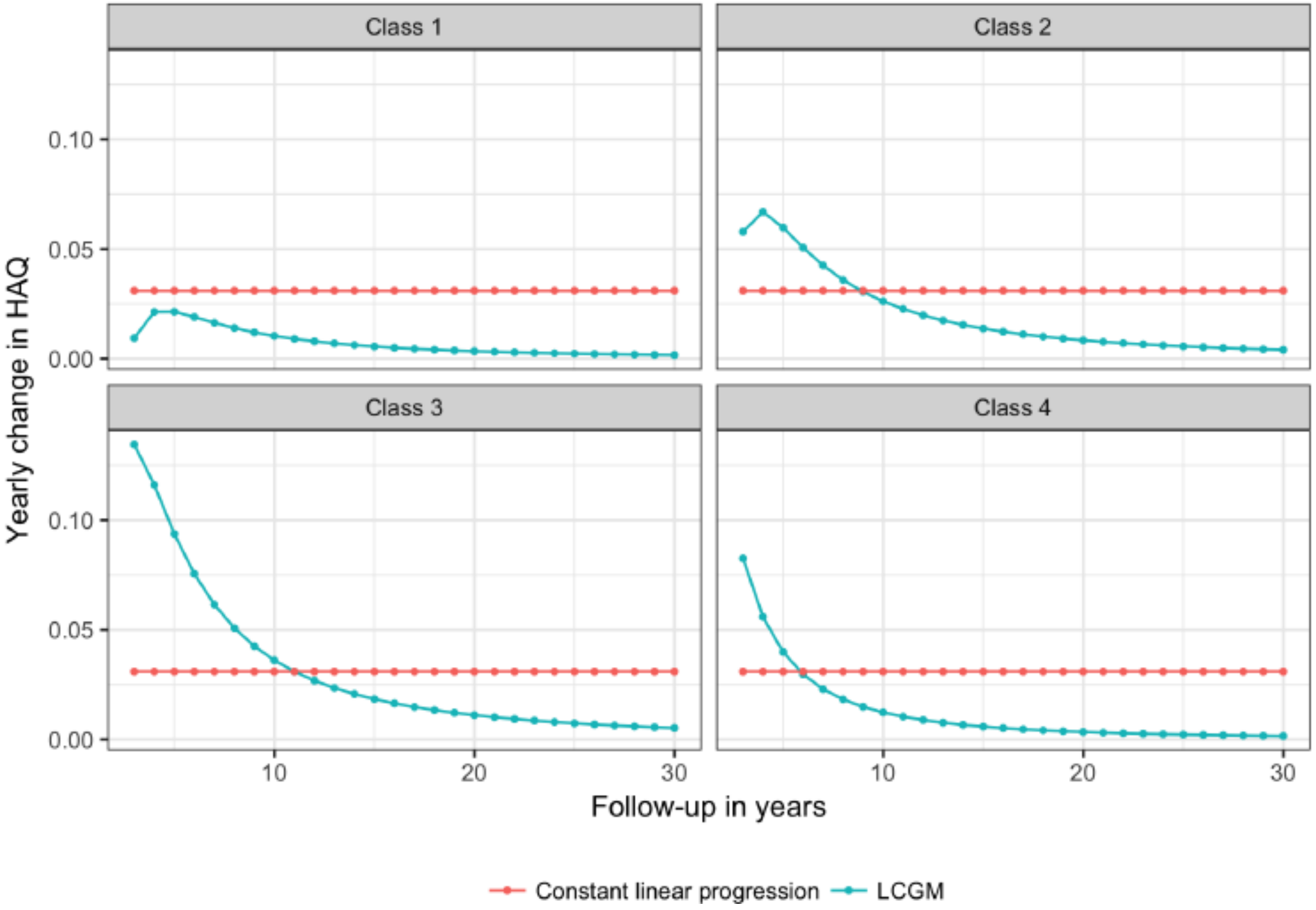
- Short-term effect of treatment on HAQ
- Causes of treatment switching
- Long-term progression of HAQ
- The probability distribution used to measure time to treatment discontinuation
- Algorithm used to simulate utility

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


AEs
6 month treatment switch
Long-term treatment discontinuation
Patient
Baseline HAQ, age, gender, disease activity
Treatment
ACR response
EULAR or disease activity
6 month HAQ reduction
HAQ progression

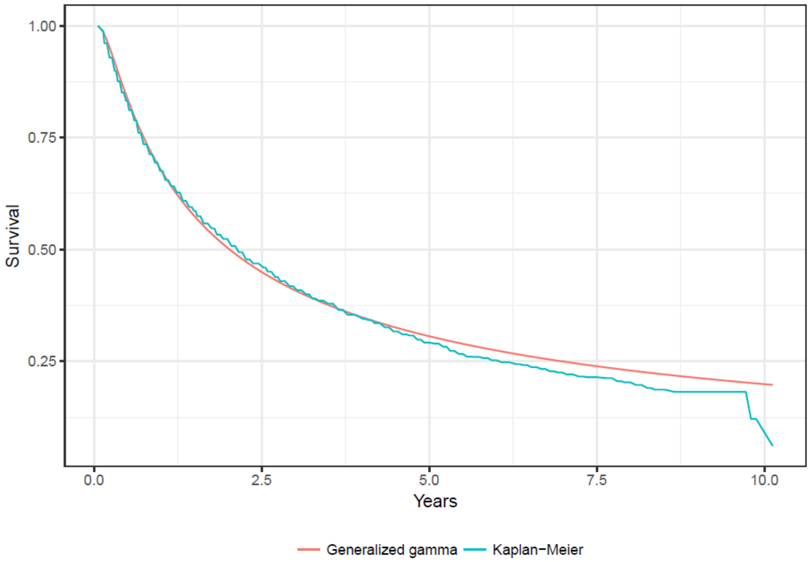
Long term progression of HAQ over time

- 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

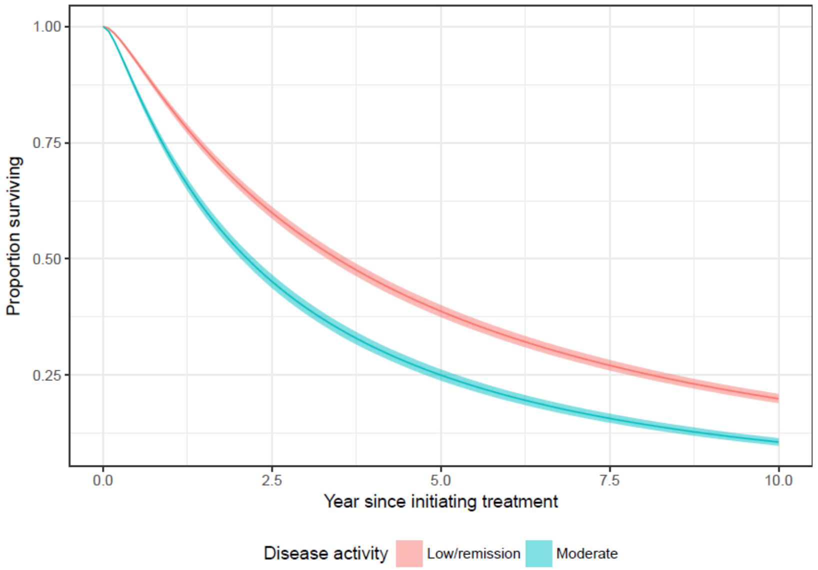


Duration of maintenance treatment

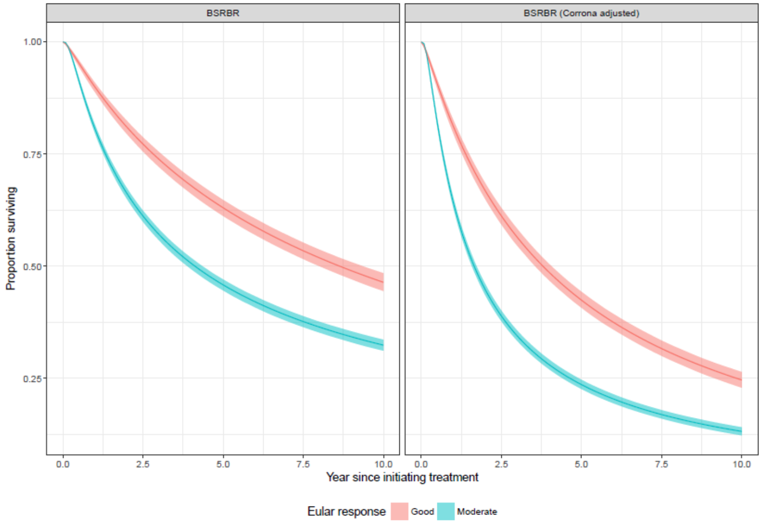
Non-stratified



By disease activity level

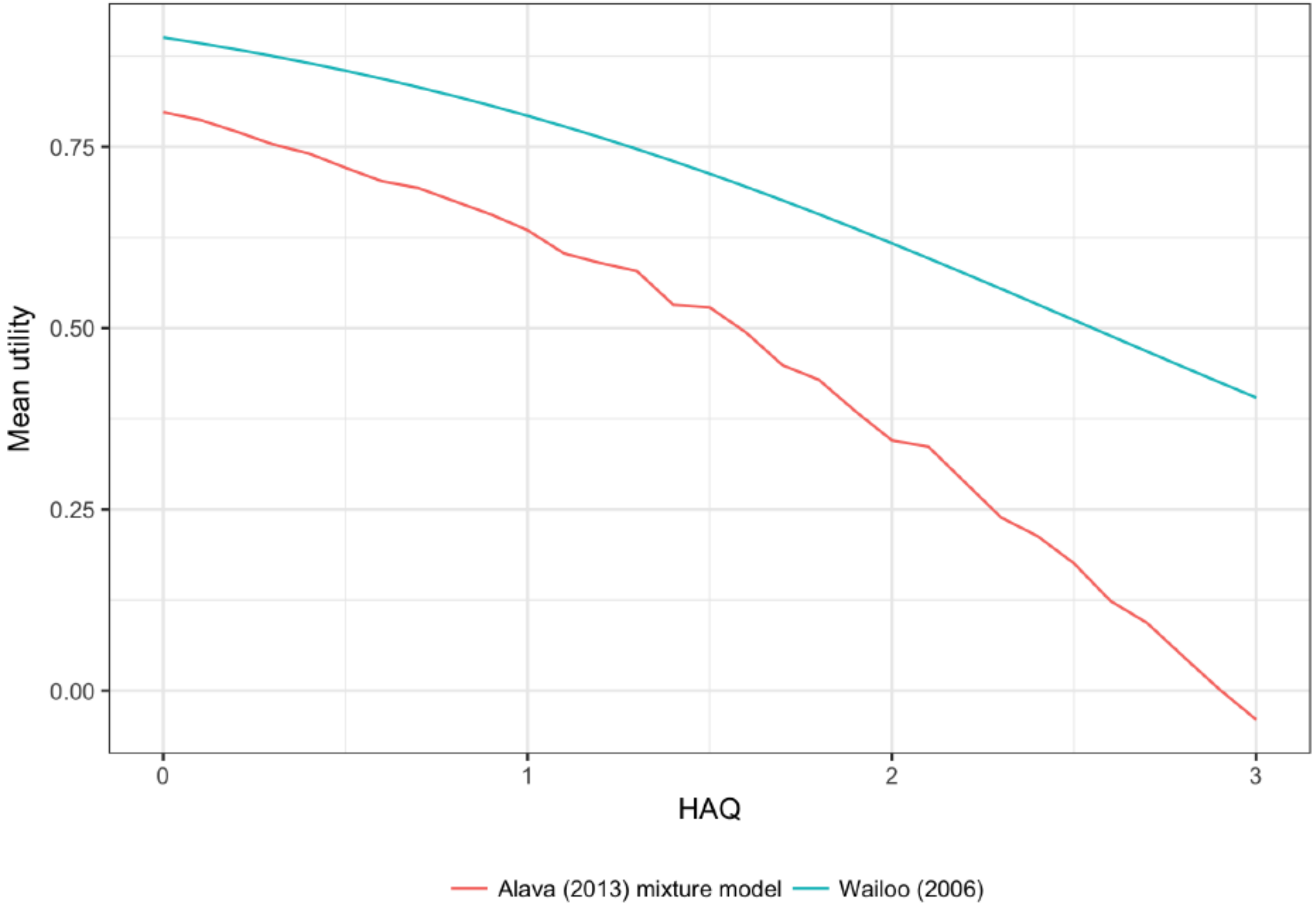


By EULAR response



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)

Model 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

- **Clinical outcomes during initial treatment phase**: ACR response, EULAR response, DAS28, SDAI, CDAI
- **Long-term clinical outcomes**: HAQ, QALYs
- **Adverse events**: number of serious infections
- **Health care sector costs**: drug acquisition and administration costs, general management and monitoring costs, adverse event costs, hospitalization costs
- **Non-health care sector costs**: productivity losses
- **Value assessment**: CEA and MCDA

Simulation

- Simulation structure
  - Discrete time individual patient simulation (IPS)
  - Probabilistic sensitivity analysis (PSA)
  - Structural uncertainty analysis
- Computationally intensive
  - Run 10,000 individual patients
  - Assume all patients survive 30 years (60 model cycles)
  - Sample 1,000 parameter sets for PSA
  - Consider 50 model structures
  - => 30 billion iterations

SECTION

3

Developing models using R

IVI-RA model development process

1. Parameter estimation using R’s packages for statistical analysis
2. Development of simulation using R and C++ (Rcpp)
3. Analysis of model output using R
4. Web applications with R Shiny

Why R?

- Vast array of statistical packages for parameter estimation (e.g., *flexsurv, rjags*) and simulation (e.g., random sampling functions)
- Easy to speed up computationally intensive code by linking R to C++ with Rcpp
- Facility for dynamic report generation (e.g., *knitr)*
- Script based languages are reproducible and transparent
- Automated code testing

Using R packages to develop models

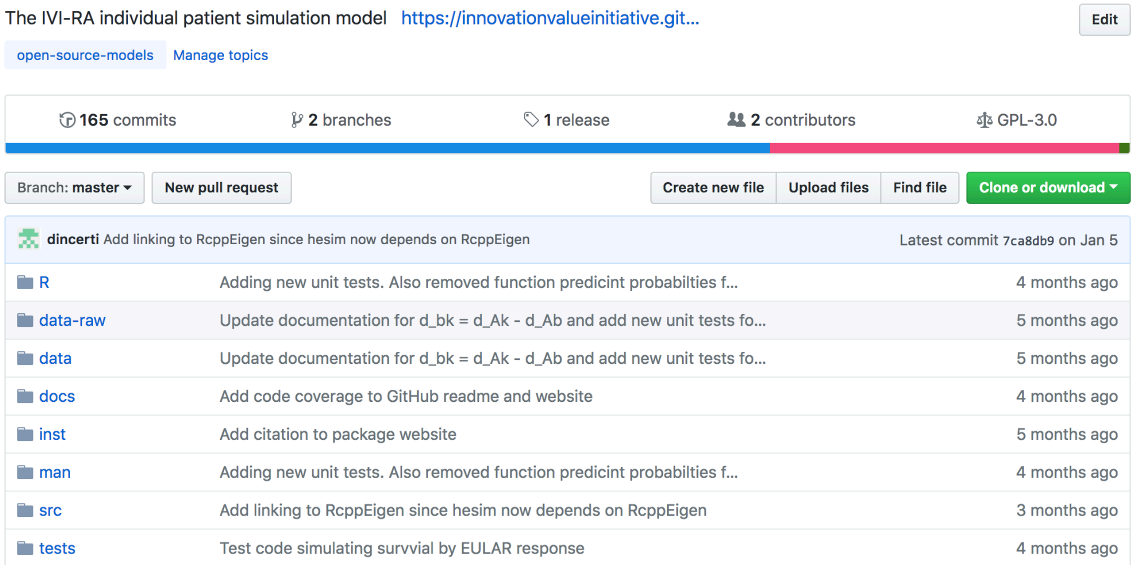
Bundles together relevant components:

- Data
- Code
- Documentation
- Testing

Easy to share with others either as an open-source package or privately

IVI-RA package 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:*** Unit testing via R package *testthat*



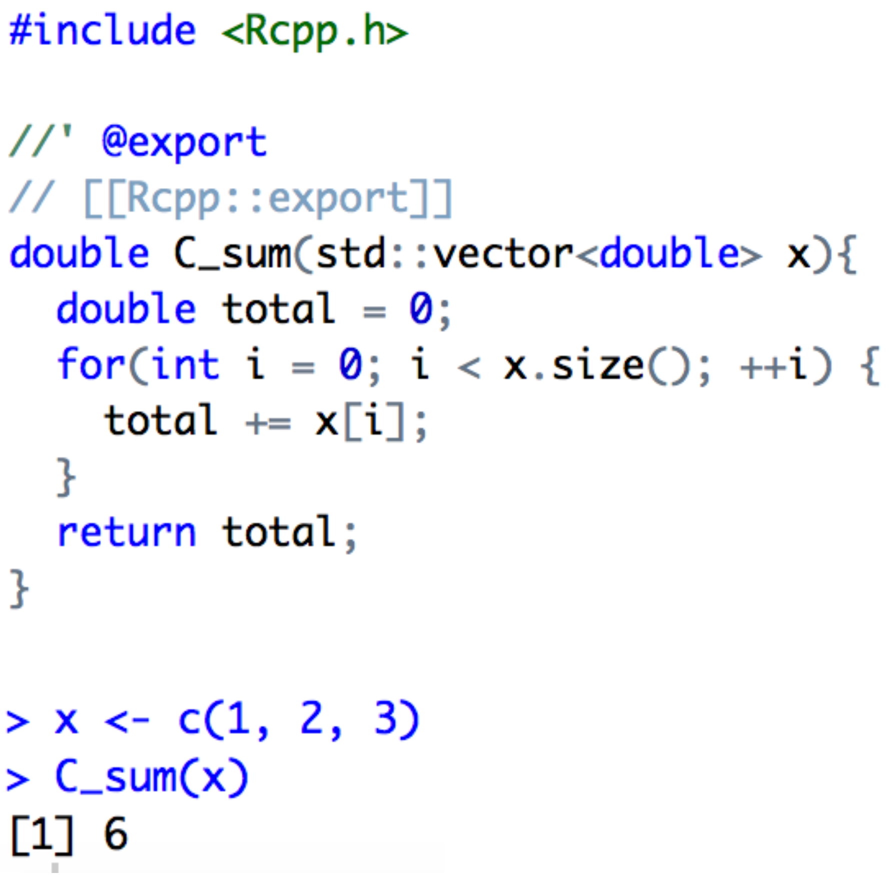
The IVI-RA individual patient simulation model https://innovationvalueinitiative.git...

dincerti Add linking to RcppEigen since hesim now depends on RcppEigen — Latest commit 7ca8db9 on Jan 5

R	Adding new unit tests. Also removed function predicint probabilties 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 probabilties f...	4 months ago
src	Add linking to RcppEigen since hesim now depends on RcppEigen	3 months ago
tests	Test code simulating survvial by EULAR response	4 months ago

Speeding up models with Rcpp

- Individual patient simulations are notoriously slow, especially when combined with probabilistic sensitivity analysis
    - Using an IPS based on the diabetes UKPDS-68 outcomes equations, McEwan et al. (2010) showed that a PSA with VBA took 13.5 hours while the same simulation with C++ took 3 minutes
- Rcpp simplifies object interchange between R and C++
- C++ code easily added within R packages



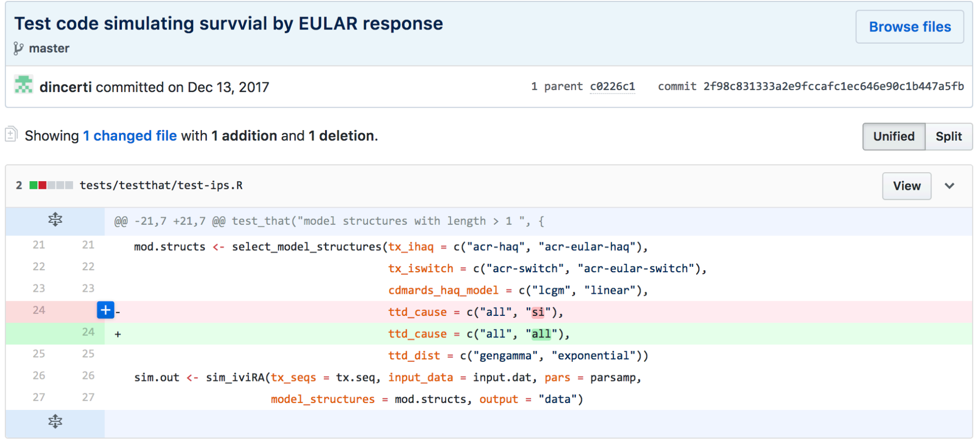
```
#include <Rcpp.h>

//' @export
// [[Rcpp::export]]
double C_sum(std::vector<double> x){
  double total = 0;
  for(int i = 0; i < x.size(); ++i) {
    total += x[i];
  }
  return total;
}
```

```
> x <- c(1, 2, 3)
> C_sum(x)
[1] 6
```

McEwan P, Bergenheim K, Yuan Y, Tetlow AP, Gordon JP. Assessing the relationship between computational speed and precision. Pharmacoeconomics. 2010 Aug 1;28(8):665-74.

Version control

- Version control helps model developers track all modifications to code over time
- Allows developers to revert to old versions or to create new “branches” in order to add new features or experiment
- The code history for the IVI-RA model is available on GitHub
- Models released can be versioned on GitHub (or on CRAN as an R package)



Test code simulating survvial by EULAR response

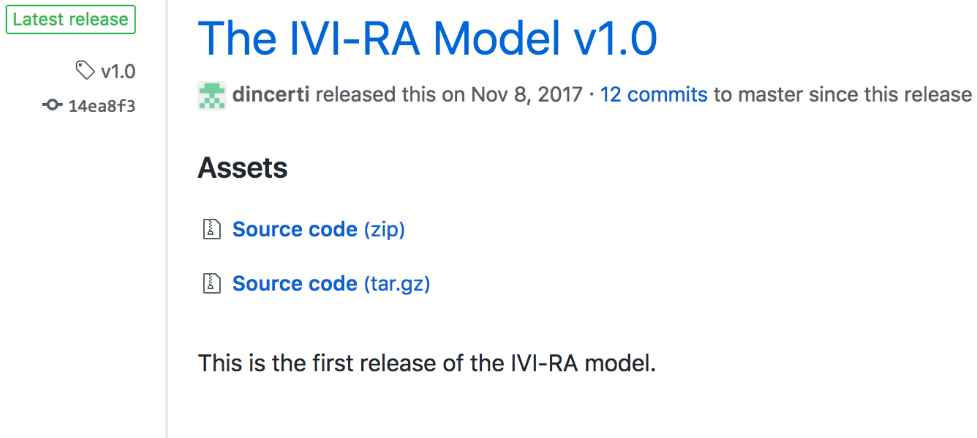
master

dincerti committed on Dec 13, 2017 1 parent c0226c1 commit 2f98c831333a2e9fccafc1ec646e90c1b447a5fb

Showing 1 changed file with 1 addition and 1 deletion.

2 tests/testthat/test-ips.R

```
@@ -21,7 +21,7 @@ test_that("model structures with length > 1 ", {
   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_cause = c("all", "all"),
                                          ttd_dist = c("gengamma", "exponential"))
   sim.out <- sim_iviRA(tx_seqs = tx.seq, input_data = input.dat, pars = parsamp,
                        model_structures = mod.structs, output = "data")
```



The IVI-RA Model v1.0

dincerti released this on Nov 8, 2017 · 12 commits to master since this release

Assets

Source code (zip)

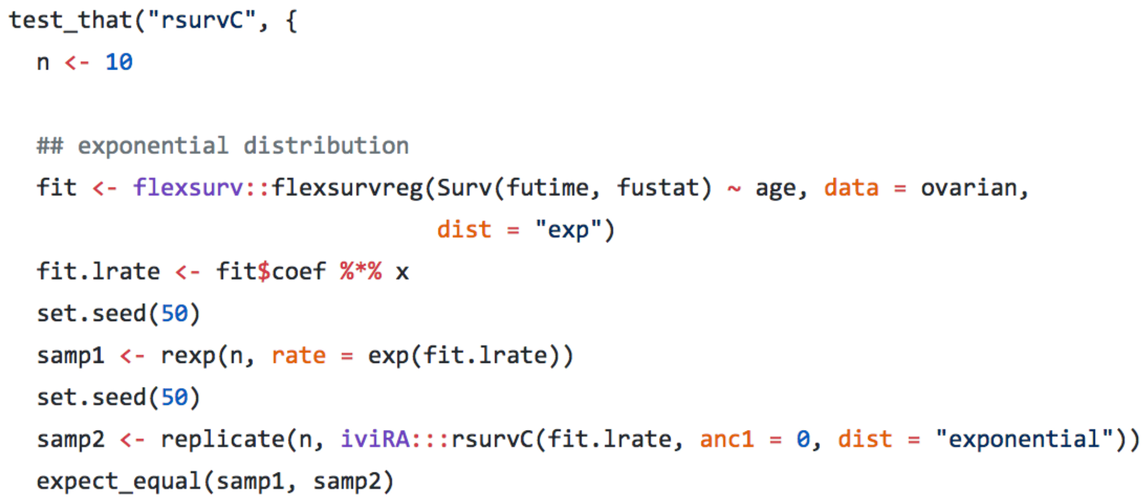
Source code (tar.gz)

This is the first release of the IVI-RA model.

Unit testing

build passing codecov 91%

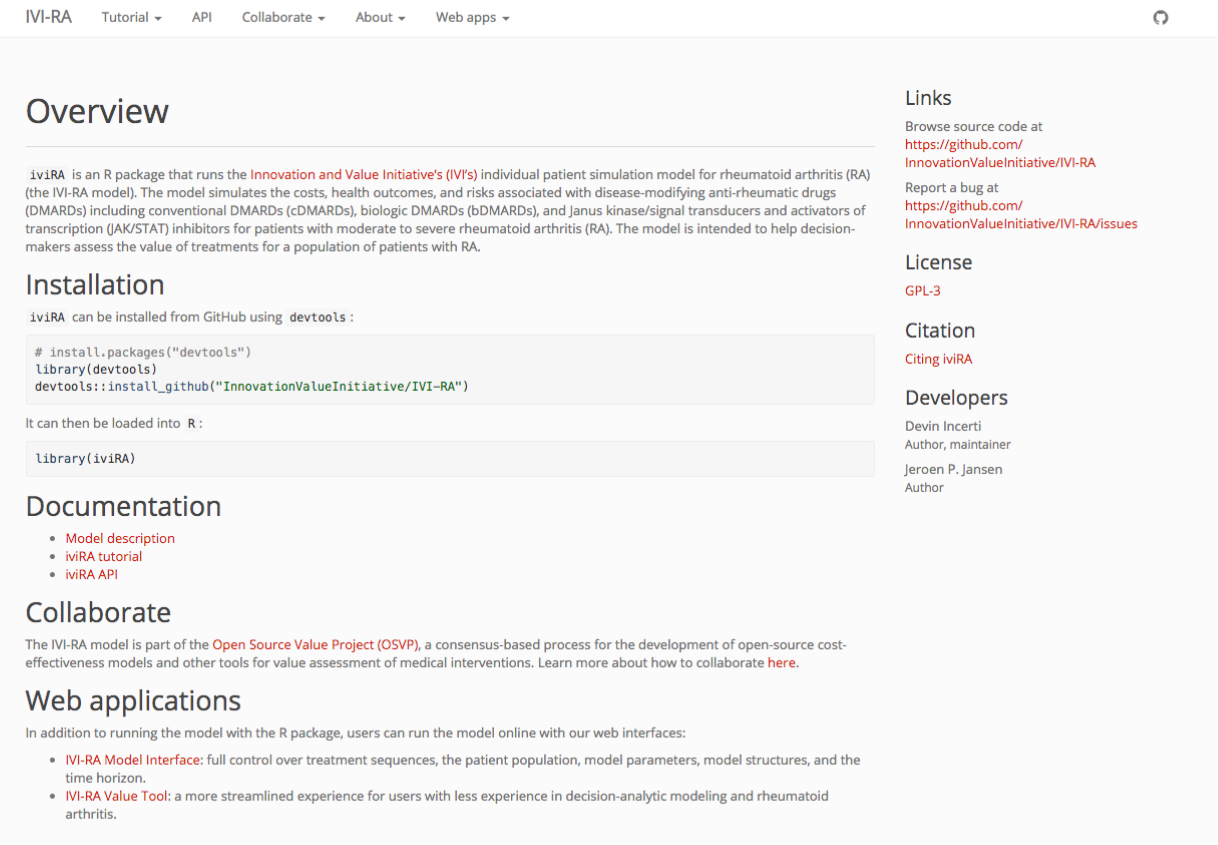
- The IVI-RA package contains hundreds of unit tests to help ensure that the code works as intended
- Each time the code is pushed (e.g., updated) to GitHub:
  - It is re-compiled and installed on an external Ubuntu machine with Travis-CI
  - codecov.io estimates the percent of the code that is covered 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)
```

Documentation with R packages

Website with *pkgdown*



Overview

`iviRA` is an R package that runs the Innovation and Value Initiative's (IVI's) individual patient simulation model for rheumatoid arthritis (RA) (the IVI-RA model). The model simulates the costs, health outcomes, and risks associated with disease-modifying anti-rheumatic drugs (DMARDs) including conventional DMARDs (cDMARDs), biologic DMARDs (bDMARDs), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) inhibitors for patients with moderate to severe rheumatoid arthritis (RA). The model is intended to help decision-makers assess the value of treatments for a population of patients with RA.

Installation

`iviRA` can be installed from GitHub using `devtools` :

```
# install.packages("devtools")
library(devtools)
devtools::install_github("InnovationValueInitiative/IVI-RA")
```

It can then be loaded into `R` :

```
library(iviRA)
```

Documentation

- Model description
- iviRA tutorial
- iviRA API

Collaborate

The IVI-RA model is part of the Open Source Value Project (OSVP), a consensus-based process for the development of open-source cost-effectiveness models and other tools for value assessment of medical interventions. Learn more about how to collaborate here.

Web applications

In addition to running the model with the R package, users can run the model online with our web interfaces:

- IVI-RA Model Interface: full control over treatment sequences, the patient population, model parameters, model structures, and the time horizon.
- IVI-RA Value Tool: a more streamlined experience for users with less experience in decision-analytic modeling and rheumatoid arthritis.

Links

Browse source code at https://github.com/InnovationValueInitiative/IVI-RA

Report a bug at https://github.com/InnovationValueInitiative/IVI-RA/issues

License

GPL-3

Citation

Citing iviRA

Developers

Devin Incerti
Author, maintainer

Jeroen P. Jansen
Author

Dynamic report with *knitr*

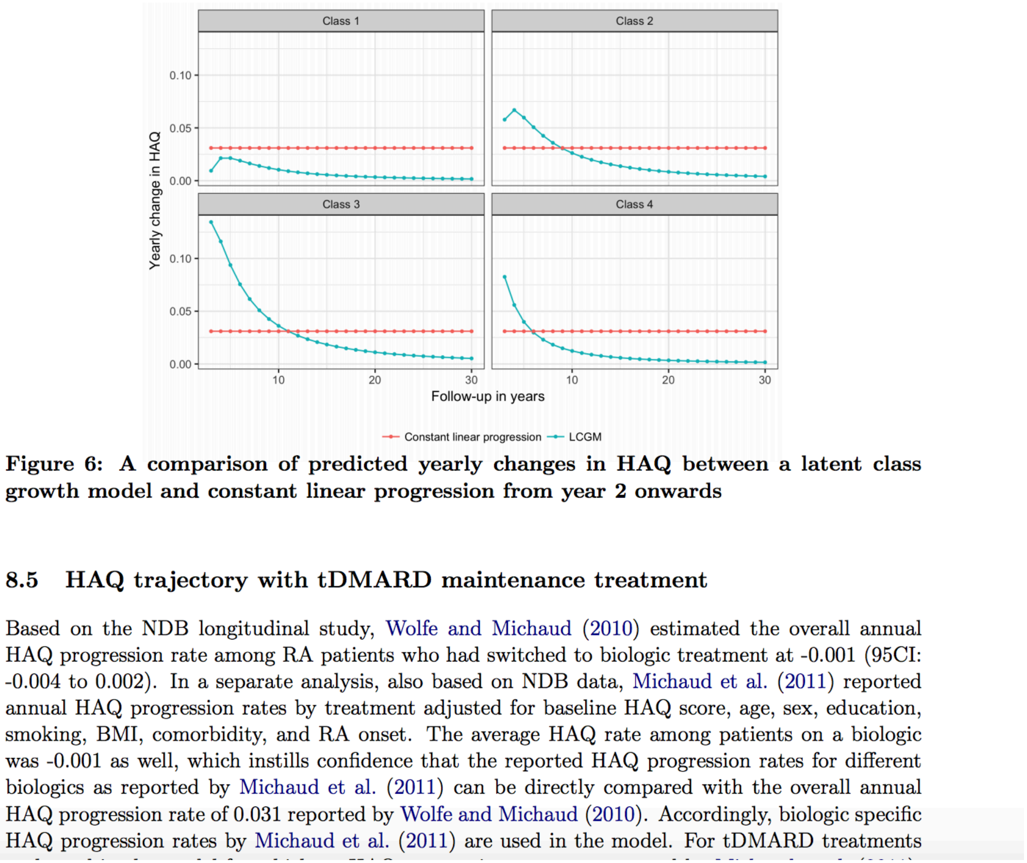


Figure 6: A comparison of predicted yearly changes in HAQ between a latent class growth model and constant linear progression from year 2 onwards

8.5 HAQ trajectory with tDMARD maintenance treatment

Based on the NDB longitudinal study, Wolfe and Michaud (2010) estimated the overall annual HAQ progression rate among RA patients who had switched to biologic treatment at -0.001 (95CI: -0.004 to 0.002). In a separate analysis, also based on NDB data, Michaud et al. (2011) reported annual HAQ progression rates by treatment adjusted for baseline HAQ score, age, sex, education, smoking, BMI, comorbidity, and RA onset. The average HAQ rate among patients on a biologic was -0.001 as well, which instills confidence that the reported HAQ progression rates for different biologics as reported by Michaud et al. (2011) can be directly compared with the overall annual HAQ progression rate of 0.031 reported by Wolfe and Michaud (2010). Accordingly, biologic specific HAQ progression rates by Michaud et al. (2011) are used in the model. For tDMARD treatments

SECTION

4

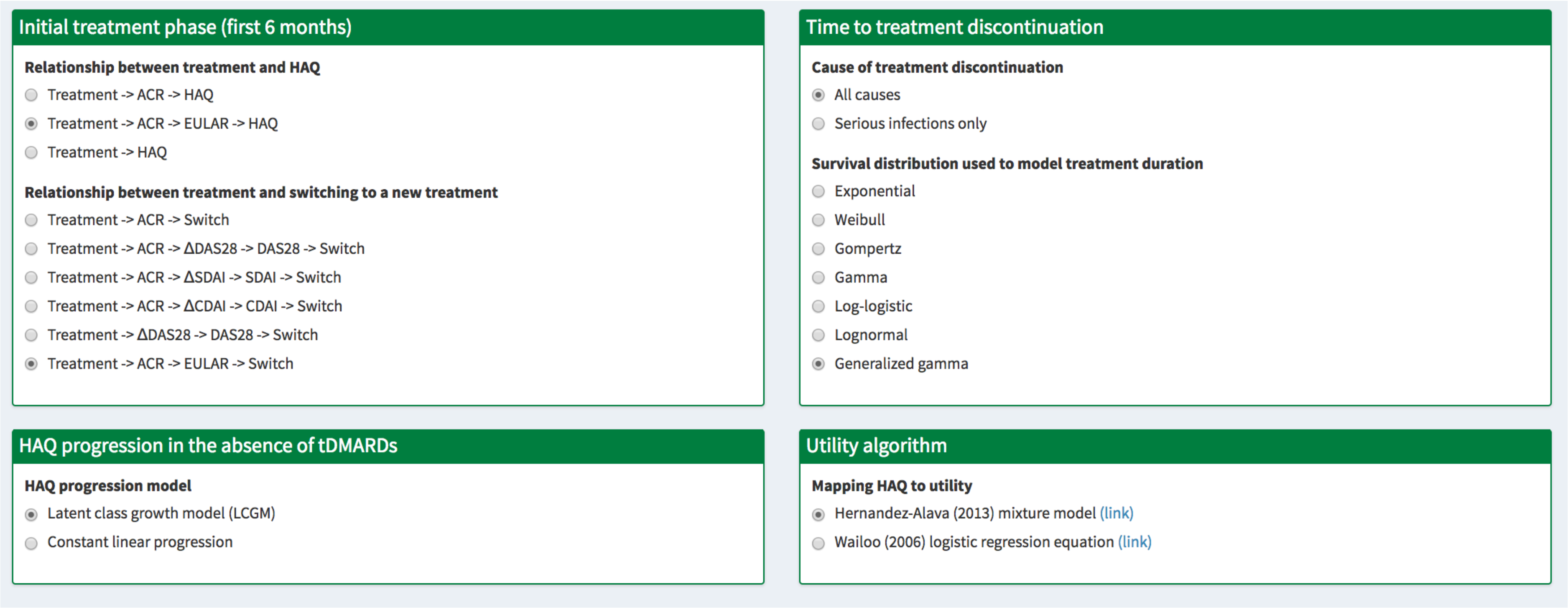
Creating web interfaces

Why do we need web interfaces?

- Translates complex models into a simpler, graphical form
- Health economists and modelers can use or evaluate models without specialized knowledge or access to a particular programming language or software platform
- Can help facilitate feedback from non-technical stakeholders and use by decision-makers
- Allows model developers to use tools fit for purpose

Allowing advanced users to modify the IVI-RA model

- Users can modify the characteristics of the population, select up to 5 treatment sequences of arbitrary length, select a model structure (below), and modify nearly all model parameters



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

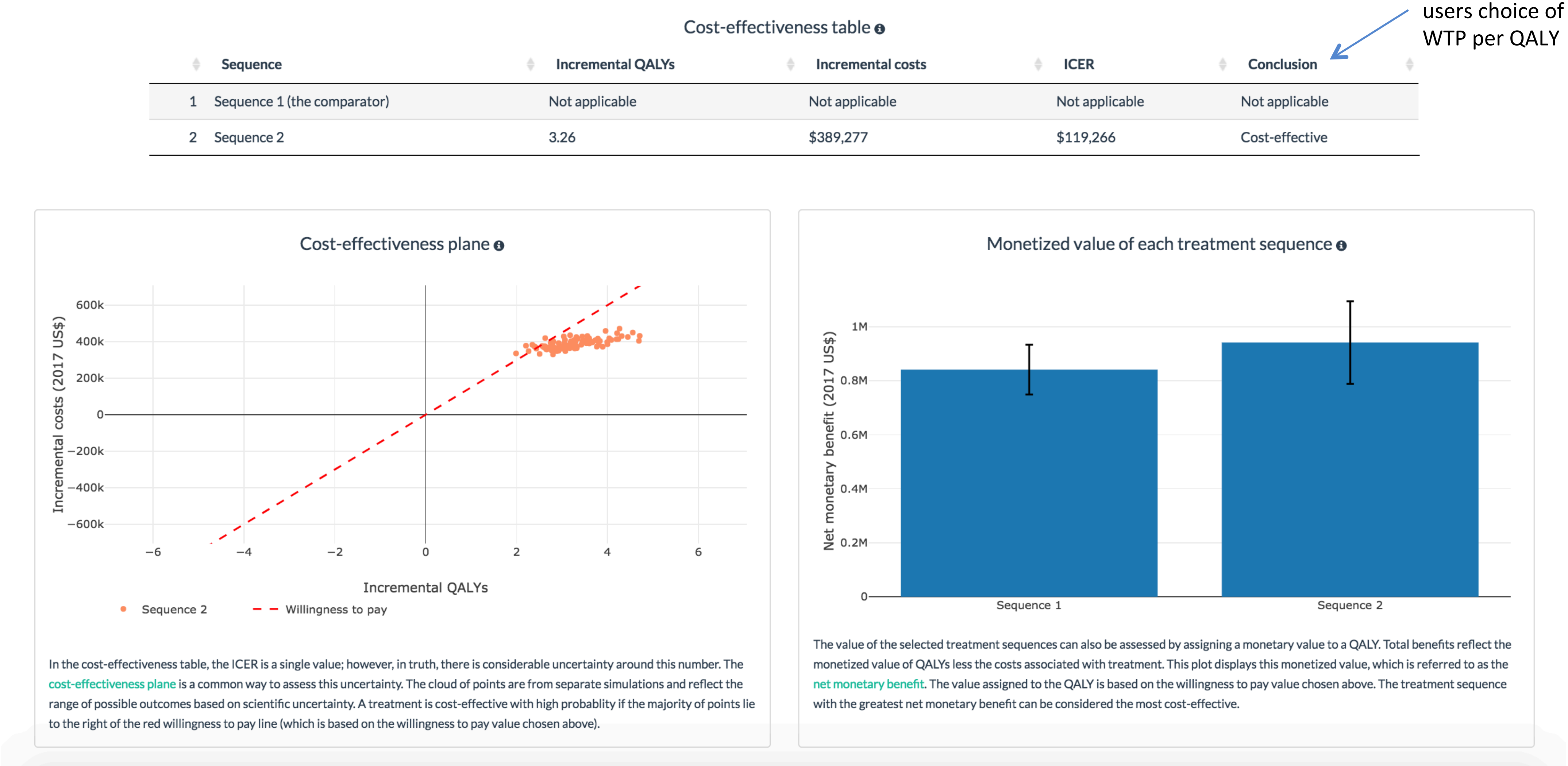
● Latent class growth model (LCGM)
○ Constant linear progression

Utility algorithm

Mapping HAQ to utility

● Hernandez-Alava (2013) mixture model (link)
○ Wailoo (2006) logistic regression equation (link)

Sample output from IVI-RA web interface



Conditional on users choice of WTP per QALY

Cost-effectiveness table

	Sequence	Incremental QALYs	Incremental costs	ICER	Conclusion
1	Sequence 1 (the comparator)	Not applicable	Not applicable	Not applicable	Not applicable
2	Sequence 2	3.26	$389,277	$119,266	Cost-effective

Cost-effectiveness plane

In the cost-effectiveness table, the ICER is a single value; however, in truth, there is considerable uncertainty around this number. The cost-effectiveness plane is a common way to assess this uncertainty. The cloud of points are from separate simulations and reflect the range of possible outcomes based on scientific uncertainty. A treatment is cost-effective with high probablity if the majority of points lie to the right of the red willingness to pay line (which is based on the willingness to pay value chosen above).

Monetized value of each treatment sequence

The value of the selected treatment sequences can also be assessed by assigning a monetary value to a QALY. Total benefits reflect the monetized value of QALYs less the costs associated with treatment. This plot displays this monetized value, which is referred to as the net monetary benefit. The value assigned to the QALY is based on the willingness to pay value chosen above. The treatment sequence with the greatest net monetary benefit can be considered the most cost-effective.

Using R Shiny to develop web interfaces

- *shiny* is an R package that allows modelers to build interactive web interfaces straight from R
- Allows modelers to develop web interfaces relatively quickly using only the R programming language
- Can be highly customized using JavaScript, HTML, and CSS
- OpenCPU is an alterative solution for R-based models that allows even more customization than Shiny

SECTION

5

Lessons learned and tools for future model development

Lessons learned

- Define your objectives
  - Does your model need to be continuously updated over time?
  - How fast does your model need to be?
  - Who is the intended audience?
  - How general does your code need to be?
- Plan before coding
  - Plan your code base carefully before you begin coding (e.g., wait until you have a defined model structure based on the available evidence base)
  - Don’t begin building a web app until you know what your target audience is looking for
- Don’t optimize code too early
  - If an optimization (e.g., speed improvement) isn’t trivially clear, don’t optimize until you can profile your code

Tools for future model development

- Currently developing an open-source R package for simulating and analyzing models with R
- Some features that may be useful
  - Generalized framework for using statistical models and patient-level data to create model structures at R level
  - Support for common models such as partitioned survival analysis and state-transition modeling (cohort, IPS), written in C++ under the hood for speed
  - Summarizing probabilistic sensitivity analyses (also look at the *bcea* R package*)*
  - Relevant functions for survival distributions at C++ level (exponential, Weibull, Gompertz, gamma, lognormal, log-logistic, generalized gamma, splines, fractional polynomials) for cases in which there is a need to create bespoke IPS models and performance is important

Q&A session

Thank you for your attention!