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A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease:
motivation, challenges and user interface

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on behalf of the SHARP Collaborative Group

Workshop on R for trial and model-based cost-effectiveness analysis

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Outline

- Motivation
- Model development
- Challenges in implementing in R
- Shiny user-friendly interface & demonstration

References:

1) Model paper: Schlackow I et al. A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease. Heart 2017. https://heart.bmj.com/content/103/23/1880

2) Model interface http://dismod.ndph.ox.ac.uk/kidneymodel/app/

Motivation: research context

- Research question: What is the cost-effectiveness of lowering cholesterol in categories of CKD patients (eg, by CKD stage and CVD risk) with statin-based treatment?
- Key data: SHARP, a RCT studying the efficacy question in a range of CKD patients
  - 9,270 participants; followed for 4.9 years
  - At entry: Age 62, 63% men; 13% smokers; 23% diabetes; 15% vascular disease; CKD stage 3B (25%), 4 (29%), 5 (14%), on dialysis (33%)
  - During the study: hospital admissions data throughout; EQ-5D-3L at study end
    - 1,736 from 6,245 pre-dialysis participants progressed to dialysis
    - 1,135 received kidney transplant
    - 1,515 experienced 1+ Major Vascular Events (MVEs)
    - 2257 died: 749 died from vascular causes

So, why R?

- Funder brief: A model fit for NICE submission (...Excel in 2010!); adaptable to other jurisdictions
- However, based on previous experience:

- Excel: inflexible for the model complexity envisaged, difficult to error-proof, slow to evaluate uncertainty
- Stata, SAS: programming structures limit flexibility; no user-friendly interface option
- R: least restrictive technically; emerging option/s (in 2010!) for input/output from Excel (ie, Excel interface of an R model)
- For an external use with large participant datasets the model might need to be programmed in a general-purpose programming language (e.g. C++) to speed execution time.

Developing the model: premises and challenges

Structural

Duality between chronic kidney and cardiovascular disease

- Chronic kidney disease progresses to more advanced stages
- Kidney disease increases risk of cardiovascular events
- Cardiovascular events may accelerate kidney disease progression

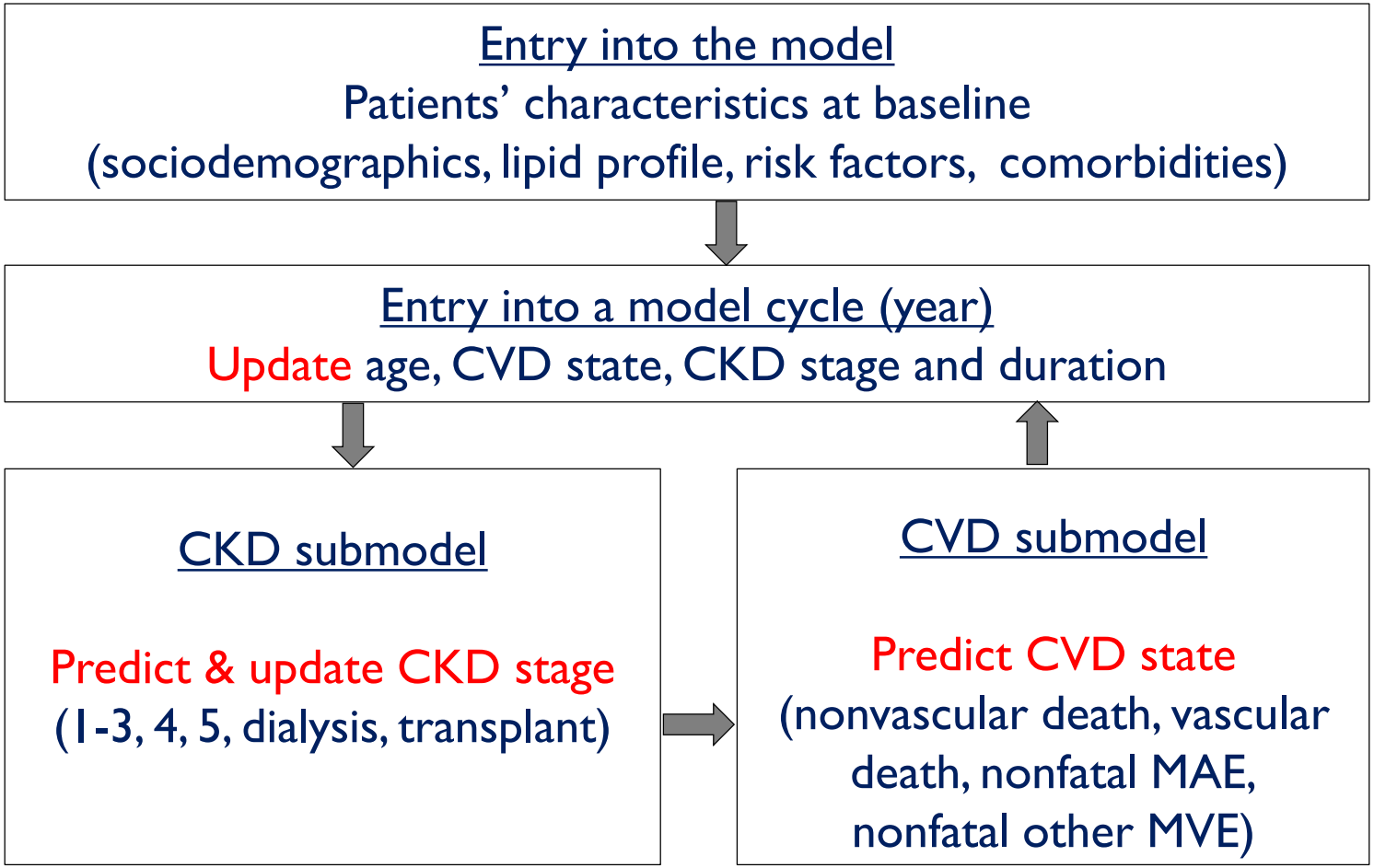
Computational

- Large number of states
- Predictions based on time-updated patient covariates

SHARP CKD-CVD model: structure

- Markov cohort model with an annual cycle of transition
  - Sub-model 1: Chronic kidney disease progression (CKD)
  - Sub-model 2: Cardiovascular disease complications (CVD)
- Backbone: A number of Risk/Cost/QoI regression equations based on SHARP participant-level data
  - 3 CVD; 2 CKD, 1 hospital cost; 1 QoL; further data (NVD; transplant failure)
- For each patient and each year, progression of CKD and major CVD complications and deaths are simulated
- Occurrence of CKD/CVD events in the model contribute to risk of subsequent such events and mortality

SHARP CKD-CVD model: structure



MAE= Major Atherosclerotic Event; MVE= Major Vascular Event

CVD risk equations

		Hazard Ratio	
		Vascular death (Exponential PH)	**Non-fatal MAE or vascular death** (Gompertz PH)
Current age	x10yrs	1.6*	1.4*
Current CKD stage (ref: stage 3B)	stage 4	1.8*	1.3*
	stage 5	2.4*	1.8*
	transplant	1.1	0.9
	dialysis (ESRD <3y)	3.4*	2.6*
	dialysis (ESRD >3y)	5.1*	3.3*
Current CV history (ref: no events)	Vasc disease at baseline	1.7*	2.0*
	MAE <1y ago	3.0*	4.3*
	MAE 1-2y ago	2.6*	3.5*
	MAE >2y ago	1.5*	2.3*
	Other MVE	4.7*	4.2*
Ancillary parameter in survival model		-	-0.0002*

VD model adjusted for Tx allocation, sex, country/ethnicity, smoking, diabetes, DBP, haemoglobin, type of renal disease
NFMAE/VD model adjusted for Tx allocation, sex, country/ethnicity, diabetes, SBP, haemoglobin, total cholesterol, HDL cholesterol, type of renal disease * $p<0.01$

Decision analytic model states

Cardiovascular states	Kidney disease states
No events (with/without prior vascular disease)	Stage 1-3
Non-fatal MAE <1y ago	Stage 4
Non-fatal MAE 1-2y ago	Stage 5
Non-fatal MAE >2y ago	Transplant
Non-fatal other MVE <1y ago	Dialysis, ESRD <3y
Non-fatal other MVE >1 ago	Dialysis, ESRD >3y
	Plus the ESRD tunnel states

Any combination of cardiovascular and kidney disease states is possible plus two death states- vascular death and non-vascular death.

6*11+2 = 68 states

SHARP CKD-CVD model: incorporating disease duality

For each person; for each year

update age and CKD duration

CKD submodel

For each possible starting state

update CVD history & CKD stage

predict possible CKD stages

update transitional probability matrix

Update distribution across possible states

CVD submodel

For each possible starting state

update CVD history & CKD stage

predict possible CVD states

update transitional probability matrix

Update distribution across possible states

SHARP CKD-CVD model: challenges in R

SHARP CKD-CVD model: challenges in R

- Initial run on 10,000 patients took >24 hours!
  - Even without uncertainty

SHARP CKD-CVD model: tips for speeding up calculations

- Employ parallel programming
  - Calculations run in parallel for several patients
  - This reduces the time by (N of cores) times
  - Even standard desktops often have 4 cores
  - R packages: foreach, parallel, doParallel:
    - Start a cluster & export functions/packages
    - Replace for (i in 1:n) {…} with foreach (i = 1:n) %dopar% {…}
    - Stop the cluster
  - NB: No parallel programming in Excel!

SHARP CKD-CVD model: tips for speeding up calculations

- Pre-calculate as much as possible, eg
  - Give unique numbers for each state (1..68)
  - For each state, record
    - Values of covariates for CVD history & CKD stage (eg state 1 is "no MVE, CKD stage 1-3b)*
    - Possible states to transition into (eg from state 1 can go into states 1, 2, 3, 4, 8 but NOT state 23 "MAE last year, CKD stage 1-3b)
    - Information is generated once and recorded externally
    - In running through the loop, the information is only referred to, but NOT re-generated
- In each loop, only run through possible transitions
  - Remove "no MAE" row if the starting state is "MAE last year"
  - Massively reduces size of the transition matrix
    - From state 1, seven columns instead of 68

*As different equations employ different covariates categories, values should be recorded separately

SHARP CKD-CVD model: tips for speeding up calculations

- Split (and pre-save) lookup datasets
  - Separate survival tables for males & females & CKD stages
- Use fixed numbers/coordinate locations instead of names
  - Read off gender from v[2] instead of v["sex"])

```
if (vX_0[2] == 1) { # if patient male
      if (stageRand %in% c("dialysis", "transplant")) # if patient ESRD
        ratesNVD_2 <- ratesNVD_M_ESRD else # if patient not ESRD
          ratesNVD_2 <- ratesNVD_M
      } else { # if patient female
            if(stageRand %in% c("dialysis", "transplant")) # if patient ESRD
              ratesNVD_2 <- ratesNVD_F_ESRD else # if patient not ESRD
                ratesNVD_2 <- ratesNVD_F
          }
```

```
### starting states
states0 <- states_info[unlist(states0_num)]
states0_lab <- sapply(states0, '[[', 1) # state names

### end states
states1 <- states_info[unlist(states1_num)]
states1_lab <-  sapply(states1, '[[', 1) # state names

### transitional matrix
MCKDrownames <- states0_lab # rows
MCKDcolnames <- states1_lab  # columns
MCKD <- matrix(nrow = length(MCKDrownames), ncol = length(MCKDcolnames),
               dimnames = list(MCKDrownames, MCKDcolnames))
MCKD[, ] <- 0

### recovering information for the starting state state0
N_CV0 <- state0[[2]] # CV part of the state
N_CKD0 <- state0[[8]] # CKD part of the state
vX_state0 <- state0[[12]] # vector of covariates corresponding to the state
```

SHARP CKD-CVD model: computational challenges

- Initial run on 10,000 patients took >24 hours!
- Simple tinkering reduced it to 50 minutes
- Most reduction came from optimising the algorithm
  - Parallel programming
  - Reducing size of transitional matrices
- Only basic R functionality was used
  - 9 packages: data manipulation (reshape2, plyr, data.table); parallel programming (foreach, snowfall, doSNOW); plotting and saving (xtable, scales, ggplot2)
  - No specific CEA packages

SHARP CKD-CVD model: user-friendly interface

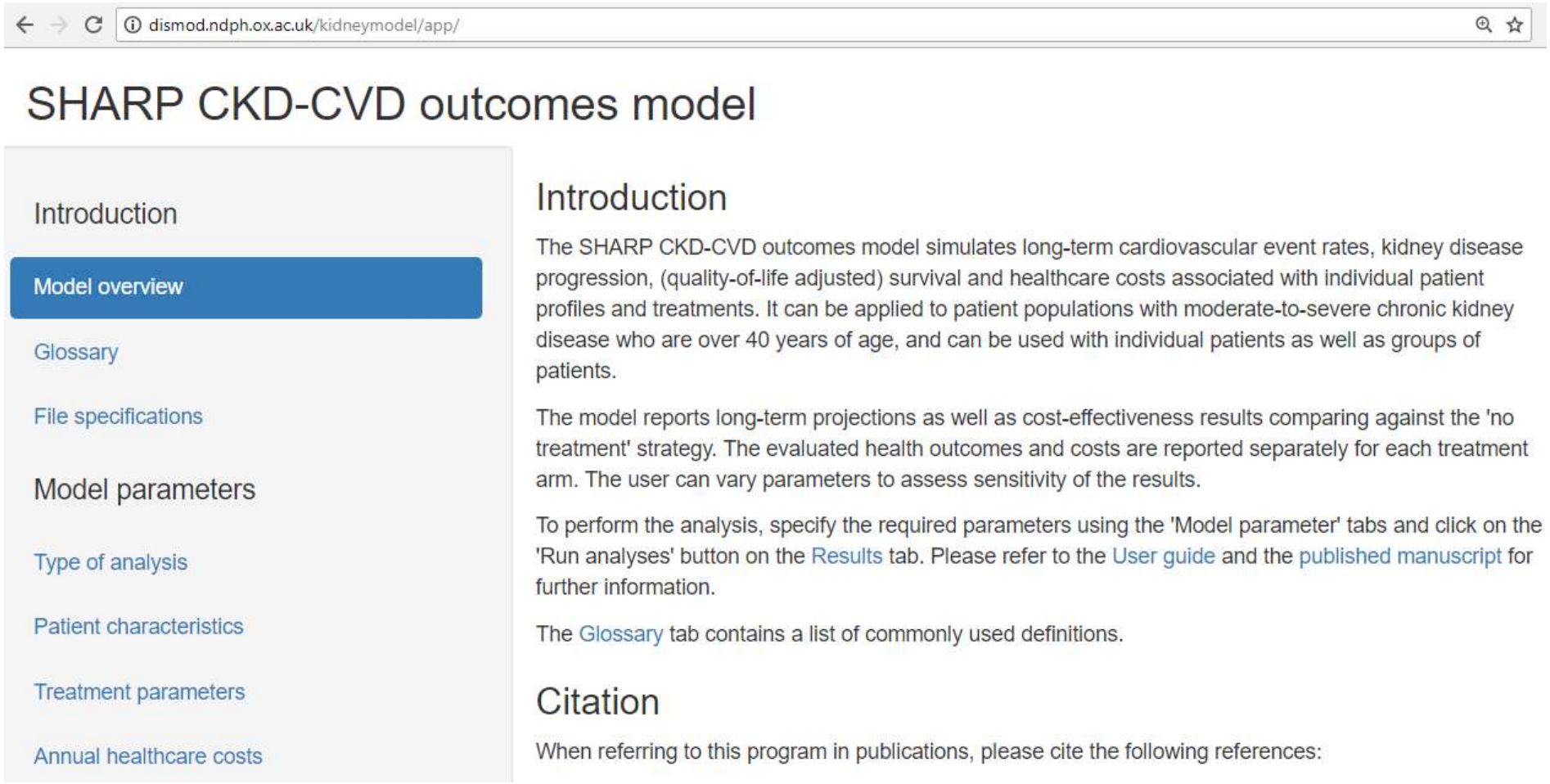
- The model to be useful for NICE, other analysts, clinicians...
- User-friendly interface accessible from anywhere
- No need for knowledge (or installation) of specialist software, eg R
- Adaptation to other population settings/countries (customising parameters)

Shiny: introduction

Shiny is an R package that allows to build interactive web applications straight from R

- ❑ The application can be accessed by clicking the link
- ❑ The user only sees the front end; no knowledge/installation of R is required
- ❑ All programs/data are located on an external server
- ❑ The front end can be modified using CSS themes, htmlwidgets, and JavaScript actions
  - ➢ Possible to insert fancy fonts, links, email addresses etc
  - ➢ Possible to implement error checking on data entry
- ❑ Further information and tutorials at https://shiny.rstudio.com/

SHARP CKD-CVD model: Shiny interface



SHARP CKD-CVD model: Shiny files structure

ui (compulsory in a separate file pre-shiny 0.10.2)

- Commands describing layout and structure of the user interface
- Definition of font styles (normal, headings, error messages)
  - Eg display error messages in red
- Action button, checkbox, date input, file input…
  - Eg numeric input or slider for age; select box for gender
  - Each entry is given a unique name
- Layout can be conditional
  - Eg display 95% CI only if performing uncertainty analysis

SHARP CKD-CVD model: Shiny files structure

ui (compulsory in a separate file pre-shiny 0.10.2)

server (compulsory in a separate file pre-shiny 0.10.2)

- Commands describing server functions definitions
- All data entered by the user are read off and passed on to corresponding variables/parameters
  - Eg define age to be the value from the numeric input called "age"
- Actions associated with data entry are defined
  - Eg perform validity check on entering numeric values; execute master function on pressing the "run" action button.

SHARP CKD-CVD model: Shiny files structure

ui (compulsory in a separate file pre-shiny 0.10.2)

server (compulsory in a separate file pre-shiny 0.10.2)

master code

- master functions performing calculations and taking parameters from server
  - Eg perform the cost-effectiveness analysis based on the user-input parameters
- Output is passed on back to ui/server to be displayed in the pre-defined user-friendly format

SHARP CKD-CVD model: Shiny files structure

ui (compulsory in a separate file pre-shiny 0.10.2)

server (compulsory in a separate file pre-shiny 0.10.2)

master code

www folder

- Contains files that are (or can be) used by the program and accessible externally
  - Eg user manual or example input/output files

SHARP CKD-CVD model: Shiny files structure

code	Today at 14:42	--	Folder
master code.R	Today at 00:43	77 KB	R Source File
shiny functions.R	8 Aug 2016 at 12:12	16 KB	R Source File
data	Today at 00:13	--	Folder
coeffs_default.Rdata	24 Jan 2017 at 15:04	3 KB	R Data File
coeffs_PSA.Rdata	24 Jan 2017 at 15:04	1.7 MB	R Data File
Default_coefficients.Rdata	24 Jan 2017 at 14:51	3 KB	R Data File
default_patient.Rdata	24 Jan 2017 at 14:55	318 bytes	R Data File
pat0.Rdata	24 Jan 2017 at 14:56	417 bytes	R Data File
patT.Rdata	24 Jan 2017 at 14:55	154 bytes	R Data File
PSA_coefficientsNew.Rdata	24 Jan 2017 at 14:51	1.9 MB	R Data File
ratesNVD.Rdata	24 Jan 2017 at 14:52	1 KB	R Data File
states_and_endpoints.Rdata	24 Jan 2017 at 15:00	7 KB	R Data File
server.R	Today at 00:46	101 KB	R Source File
ui.R	Today at 00:43	30 KB	R Source File
www	Today at 00:13	--	Folder
2014_UK_CKD_NVD.csv	28 Jun 2016 at 15:01	1 KB	comma...values
default_patient.csv	24 Jan 2017 at 14:55	320 bytes	comma...values
example_input.csv	10 Apr 2017 at 12:47	429 bytes	comma...values
example_output_CE_ind.csv	10 Apr 2017 at 12:58	3 KB	comma...values
example_output_CE_PSA_ind.csv	10 Apr 2017 at 16:47	10 KB	comma...values
example_output_CE_PSA_sum.csv	10 Apr 2017 at 16:47	4 KB	comma...values
example_output_CE_sum.csv	10 Apr 2017 at 12:57	1 KB	comma...values
example_output_LP_ind.csv	10 Apr 2017 at 12:59	2 KB	comma...values
example_output_LP_PSA_ind.csv	10 Apr 2017 at 15:33	3 KB	comma...values
example_output_LP_PSA_sum.csv	10 Apr 2017 at 15:33	1 KB	comma...values
example_output_LP_sum.csv	10 Apr 2017 at 12:58	440 bytes	comma...values
glossary.pdf	21 Jul 2016 at 12:19	10 KB	PDF document
userguide.pdf	10 Apr 2017 at 17:02	2.4 MB	PDF document

SHARP CKD-CVD model: Shiny interface

http://one-elevenbooks.com/shiny-or-the-truth/

http://dismod.ndph.ox.ac.uk/kidneymodel/app/

Discount cost-effectiveness results

Long-term projections in the control group (cumulative probabilities per 1,000 participants)

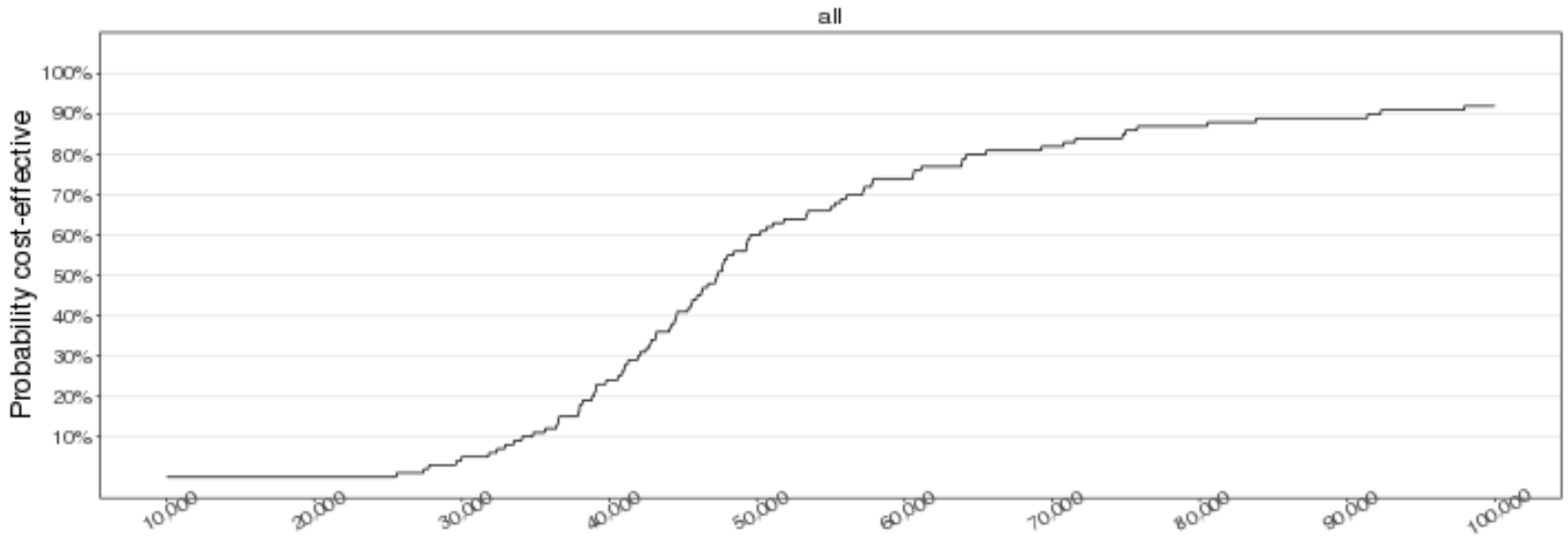
	MVE or VD	RRT	Vascular deaths	All deaths
At 5 years	184 (159, 213)	409 (357, 444)	57 (44, 76)	205 (194, 222)
At 10 years	281 (244, 319)	643 (594, 683)	118 (92, 155)	415 (398, 438)
Over simulation duration	419 (358, 501)	884 (826, 935)	292 (225, 379)	907 (897, 918)

Long-term projections in the treatment group (cumulative probabilities per 1,000 participants)

	MVE or VD	RRT	Vascular deaths	All deaths
At 5 years	169 (138, 193)	407 (355, 439)	51 (37, 70)	200 (189, 216)
At 10 years	263 (214, 299)	638 (593, 675)	106 (81, 140)	407 (389, 429)
Over simulation duration	397 (328, 477)	877 (813, 927)	271 (207, 371)	905 (896, 915)

Incremental cost-effectiveness over the simulation duration (results per 1,000 participants)

LYs gained	QALYs gained	Incremental hospital costs	Treatment costs	Cost per LY gained	Cost per QALY gained
135 (-4, 279)	107 (22, 227)	698,152 (-416,384, 1,306,000)	5,074,512 (4,904,776, 5,201,336)	42,646 (20,617, 304,068)	54,085 (27,412, 179,555)



SHARP CKD-CVD model: conclusions and more challenges

Conclusions:

- SHARP CKD-CVD model is a novel resource for evaluating health outcomes and cost-effectiveness of interventions in CKD
- Efficient coding is important and much can be achieved using basic functionality only
- The model has a user-friendly web-based and freely available interface
- The user can adapt model with enter their own parameter values and perform calculations in different settings
- The model is already being used externally by others!

SHARP CKD-CVD model: conclusions and more challenges

Further/remaining challenges:

- To further increase speed of execution
  - Particular problem when running uncertainty
  - Re-write in another language, eg C?
  - Re-design the model structure? Eg fewer states; fewer covariates; different endpoints; move away from cohort simulation?
- Day-to-day support
  - Replying to queries, bug fixing
  - R/package updates may break everything!

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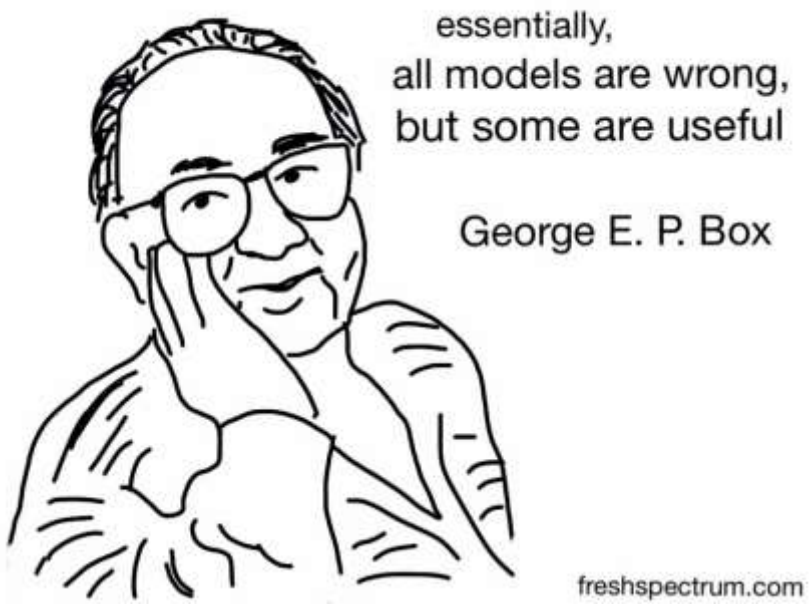
SHARP CKD-CVD model



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