MSD

R for HTA Conference 2024

An R package to inform structural assumptions for three state oncology cost-effectiveness models and examine the impact of adjusting for background mortality (psm3mkv)

Dominic Muston

Merck & Co., Inc., Rahway, NJ, USA

Publication and *psm3mkv* R package provide tools to evaluate the efficiency and fit of alternate three state model structures in oncology

Paper in *Applied Health Economics and Health Policy* describes approach, provides an example (KEYNOTE-826)

Applied Health Economics and Health Policy
https://doi.org/10.1007/s40258-024-00884-2

PRACTICAL APPLICATION

Informing Structural Assumptions for Three State Oncology Cost-Effectiveness Models through Model Efficiency and Fit

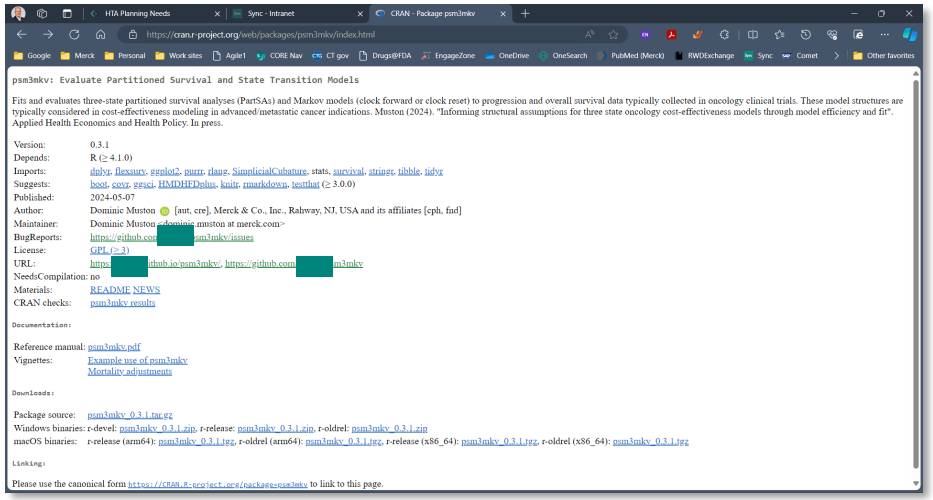
Dominic Muston[1]

Accepted: 8 April 2024

Abstract
The characteristics and relative strengths and weaknesses of partitioned survival models (PSMs) and state transition models (STMs) for three state oncology cost-effectiveness models have previously been studied. Despite clear and longstanding economic modeling guidelines, more than one structure is rarely presented, and the choice of structure appears correlated more with audience or precedent than disease, decision problem, or available data. One reason may be a lack of guidance and tools available to readily compare measures of internal validity such as the model fit and efficiency of different structures, or sensitivity of results to those choices. To address this gap, methods are presented to evaluate the fit and efficiency of three structures, with an accompanying R software package, *psm3mkv*. The methods are illustrated by analyzing interim and final analysis datasets of the KEYNOTE-826 randomized controlled trial. At both interim and final analyses, the STM Clock Reset structure provided the best and most efficient fit. Structural uncertainties had been reduced from interim to final analysis. Beyond measures of internal validity, guidelines highlight the importance of reflecting all available data, avoiding model selection purely on the basis of goodness of fit and strongly considering external validity. The method and software allow modelers to more easily evaluate and report model fit and efficiency, examine implicit assumptions, and reveal sensitivities to structural choices.

Package *psm3mkv* is available on CRAN

```
install.packages("psm3mkv")
```



Dependencies include:

- Considerable use of *flexsurv*
- *SimplicialCubature* for some double integrations required in calculating restricted mean durations in STMs
- Various tidyverse packages (*dplyr*, *purrr*, *ggplot2*, *tibble*, *stringr*, *tidyr*)

R code for this session

```
install.packages("psm3mkv")

library(psm3mkv)

vignette("mortality-adjustments", package="psm3mkv")
```

Outline of general approach

1. Obtain patient-level data
- For each patient, we must know date of progression (or censoring) and death (or censoring)
- Package requires a dataset of TTP, PFS and OS; checks consistency

2. Fit distributions to 6 x endpoints: TTP, PPD, PFS, OS, PPS-CF (time from baseline), PPS-CR (time from progression)
- Parametric, Two-piece parametric, Royston-Parmar splines

3. Select best and most valid fits to each endpoint (more manual)

4. Calculate likelihood and AIC/BIC: PSM-simple, PSM-complex, STM-CF, STM-CR
- PSM-simple: $h_{TTP}(t) = (ne_{TTP} / ne_{PFS}) . h_{PFS}(t)$

Fit (likelihood)

Efficiency (AIC/BIC)

5. Draw membership probabilities vs time (some require numerical integration)

6. Calculate Restricted Mean Durations for PF, PD, OS for each structure (package uses additional numerical integrations)
- Standard errors can be calculated by bootstrap

Structural sensitivity

How does this patient-level analysis differ from a cost-effectiveness model?
- Discounting (added to RMD calculation)
- Constraining for background mortality led to: `vignette("background-mortality")`

Abbreviations: AIC – Akaike Information Criterion, BIC – Bayesian Information Criterion, CF – clock forward, CR – clock reset, $h_x(t)$ – hazard function of endpoint x with respect to time t, "ne" – number of events, OS – overall survival, PD – progressive disease, PF – progression free, PFS – progression-free survival, PPS – post-progression survival, RMD – restricted mean duration, TTP – time to progression.

What do we mean by constraining to background mortality?

1. Constraining only the survival function

- Assumes background mortality is relevant to this population, but not reflected in unadjusted model
- Simple and has been used in at least one recent NICE TA (821)
- Does not ensure that the mortality hazard is at least as great as background mortality hazard

$$S_{adj}(t) = \text{Min}\,[S_{unadj}(t), S_{gen}(t)\,]$$

2. Constraining the hazard function

- Assumes background mortality is relevant to this population, but not reflected in unadjusted model
- Directly ensures that mortality hazard is at least as great as background mortality hazard

$$h_{adj}(t) = \text{Max}\,[h_{unadj}(t), h_{gen}(t)\,]$$

3. Excess hazard modeling

- Model the hazard of mortality in excess of an assumed background mortality
- When making projections in cost-effectiveness models, additionally apply relevant background mortality
- May add unnecessary complexity if background mortality between populations is similar: "Lifetable misspecification had minimal effect on RMST differences"

See Sweeting et al, 2023

Abbreviations: $h_x(t)$ – hazard function of endpoint x with respect to time t, NICE – National Institute of Health and Care Excellence, $S_x(t)$ – survival function of endpoint x with respect to time t, TA – technology appraisal

Application of Method Two in psm3mkv

Need to move from continuous/integral methods to discretized calculations

- Where there is no background mortality adjustment, discretized methods were only slightly quicker than continuous/integral methods in this example
- Constraint is applied to mortality probabilities calculated for each timestep, specific to structure/method

Calculation steps

1. First derive state membership probabilities of PF and PD in each timestep
2. Estimate the pre-progression mortality probability for each timestep according to the model structure/assumptions
   - Probabilities are specific to PSM-Simple, PSM-Complex, STM-CF, STM-CR methods
3. Derive the post-progression mortality probability for each timestep (balancing OS)
4. Calculate the pre- and post-progression mortality probabilities constrained by background mortality
   - Probabilities should be at least as great as background mortality at that timestep
5. Recalculate membership probabilities using constrained mortality
6. Calculate total RMD of PF and PD over given horizon, with given discount rate

Abbreviations: CF – clock forward, CR – clock reset, $h_x(t)$ – hazard function of endpoint x with respect to time t, OS – overall survival, PD – progressive disease, PF – progression free, PSM – partitioned survival model, RMD – restricted mean duration, STM – state transition model, TTP – time to progression.

Results from illustrative dataset

State transition model, clock forward

Model	RMD in PF (weeks)	Change (weeks)	RMD alive (weeks)	Change (weeks)
No mortality constraint, integral methods	270.2	-	389.9	-
No mortality constraint, discretized calculations	270.1	-0.1	389.8	-0.1
Mortality constraint, discretized calculations	230.1	-40.1	337.7	-52.2

Observations:

- The discretized method results were very close to the integral method results
- The mortality constraint reduced time in PF by 40.1 weeks (14.8%) and time alive by 52.2 weeks (13.3%)
- PPS was reduced by 12.1 weeks (10.1%) from 119.7 to 107.6 weeks

Abbreviations: PF – progression free, PF – progression-free, PD – progressive disease, PPS – post-progression survival, RMD – restricted mean duration,

Results from illustrative dataset

State transition model, clock reset

Model	RMD in PF (weeks)	Change (weeks)	RMD alive (weeks)	Change (weeks)
No mortality constraint, integral methods	270.2	-	393.9	-
No mortality constraint, discretized calculations	270.1	-0.1	393.8	-0.1
Mortality constraint, discretized calculations	230.1	-40.1	341.6	-52.3

Observations:

- Results for PF match those for the STM-CF model, but OS is 4 weeks longer for STM-CR integral methods
- The discretized method results were very close to the integral method results
- The mortality constraint reduced time in PF by 40.0 weeks (14.8%) and time alive by 52.2 weeks (13.3%)
- PPS was reduced by 12.2 weeks (9.9%) from 123.7 to 111.5 weeks

Abbreviations: CF – clock forward, CR – clock reset, PF – progression free, PD – progressive disease, PPS – post-progression survival, RMD – restricted mean duration, STM – state transition model

Results from illustrative dataset

Partitioned survival model

Model	RMD in PF (weeks)	Change (weeks)	RMD alive (weeks)	Change (weeks)
No mortality constraint, integral methods, simple PSM	274.4	-	392.7	-
No mortality constraint, discretized calculations, simple PSM	274.3	-0.1	392.6	-0.1
Mortality constraint, discretized calculations, simple PSM	235.4	-39.0	340.9	-51.8
Mortality constraint, discretized calculations, complex PSM	231.0	-43.4	334.7	-58.0

Observations:

- Results for OS are very similar to the STM-CR model, but PF durations are a little greater
- The discretized method results were very close to the integral method results
- For PSM-Simple: The mortality constraint reduced time in PF by 38.9 weeks (14.1%), and PPS by 12.8 weeks (10.8%)
- For PSM-Complex: Estimates of mean time in PF and alive were lower than PSM-Simple

Abbreviations: CF – clock forward, CR – clock reset, PF – progression free, OS – overall survival, PSM – partitioned survival model, RMD – restricted mean duration, STM – state transition model

What can we take from this?

The effect of constraining by background mortality depends on:

- The data you are fitting, and the lifetable and SMR you are assuming for background mortality
  - The example shown is merely illustrative
- The cost-effectiveness model structure (PSM, STM-CF, STM-CR), including the chosen structure for modeling of pre vs post-progression mortality (Simple vs Complex)
  - In this case, there was limited structural sensitivity, although PSM-Complex gave slightly lower estimate
  - Paper showed there was structural sensitivity in KN-826 Interim Analysis, less at Final Analysis
- How exactly the constraining assumption is made
  - In this case, this might have mattered more than the model structure (Time in PF and OS varied little by structure)
  - Should we avoid constraining only the survival function (Method 1)?
  - When do we need to model excess hazard explicitly (Method 3)?

Conclusions and Next Steps

Further research will be valuable to identify best practices in methods of and reporting for RMST estimates allowing for background mortality

- Ideally, we would want to compare long-term country-specific projections with corresponding real-world data, adjusting for baseline differences in the populations
  - Could the projections be validly improved by alternate methods of accounting for background mortality? Or is this just overfitting?
  - Could separating disease-specific mortality from all-cause help? Or not, given challenges in assigning cause of death.
- When is modeling excess hazard modeling necessary – and when is it just excessive?
- How should mortality adjustments 'properly' be made in economic models? Are survival constraints alone ok (Method 1)?
- What background mortality should be used? Cohort vs Calendar life tables. SMR value to assume.

Also, would very much value feedback on the package

- Can it provide an additional quality check to spreadsheet-derived calculations? Does it provide a basis to simplify/reduce the calculations or options expected in spreadsheet-derived cost-effectiveness models?
- Consider adding more endpoint modeling options (dependent treatment effects, cure models, fractional polynomials, M-splines)
- Consider links to other powerful packages, e.g. Jackson's *survextrap*

Abbreviations: RMST – restricted mean survival time

With thanks to …

Ruifeng Xu (Merck & Co., Inc., Rahway, NJ, USA) and **Abdel Hmissi** (MSD, Switzerland) for their assistance in preparing and analyzing the KEYNOTE-826 trial dataset

Ross Maconachie (MSD (UK) Limited, London, UK), **Ralph Insinga** (Merck & Co., Inc., Rahway, NJ, USA), **Robert Hettle** (AstraZeneca, Cambridge, UK), and the **reviewers and editor** of *Applied Health Economics and Health Policy* for careful review and constructive comments

Nan Xiao and **John Blischak** (Merck & Co., Inc., Rahway, NJ, USA) for advice on R programming, and guidance on the package submission to CRAN

Niall Davison and **Brad Kievet** of Maple Health Group for their review of the R package code and their careful documentation of issues

Matt Monberg and **Don Yin** (Merck & Co., Inc., Rahway, NJ, USA) for support and encouragement for this work

and to the **patients and investigators of the KEYNOTE-826 trial**.

References

Bullement A, Cranmer H, Shields GE. A Review of Recent Decision-Analytic Models Used to Evaluate the Economic Value of Cancer Treatments. *Applied Health Economics and Health Policy* (2019) 17:771–780. https://doi.org/10.1007/s40258-019-00513-3

Jackson, C. survextrap: a package for flexible and transparent survival extrapolation. *BMC Med Res Methodol* 23, 282 (2023). https://doi.org/10.1186/s12874-023-02094-1

Jackson C. survextrap: a package for flexible and transparent survival extrapolation. R for HTA conference 2023. https://www.youtube.com/watch?v=dV90__idtQ4

Muston D. Informing structural assumptions for three state oncology cost-effectiveness models through model efficiency and fit. *Applied Health Economics and Health Policy*, 2024. https://doi.org/10.1007/s40258-024-00884-2

Muston D. psm3mkv: Fit and Evaluate Three-State Partitioned Survival Analysis and Markov Models to Progression-Free and Overall Survival Data. https://CRAN.R-project.org/package=psm3mkv

NICE. Technology Appraisal 281, 2022. Avalglucosidase alfa for treating Pompe disease. https://www.nice.org.uk/guidance/ta821

Sweeting MJ, Rutherford MJ, Jackson D, Lee S, Latimer NR, Hettle R, Lambert PC. Survival Extrapolation Incorporating General Population Mortality Using Excess Hazard and Cure Models: A Tutorial. *Med Decis Making*. 2023 Aug;43(6):737-748. https://doi.org/10.1177/0272989X231184247

Woods B, Sideris E, Palmer S, Latimer N, Soares M, Partitioned Survival and State Transition Models for Healthcare Decision Making in Oncology: Where Are We Now? Value In Health. 2020; 23(12): 1613-21. https://doi.org/10.1016/j.jval.2020.08.2094

Thank you

Dominic Muston

e: dominic.muston@merck.com

Health Economics and Decision Sciences

Merck & Co., Inc., Rahway, NJ, USA