Methods of multi-indication evidence synthesis for health technology assessment: a simulation study

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This work was funded by a Medical Research Council (MRC) better methods better research grant MR/W021102/1.

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Simulation study

Overview

- What is multi-indication meta-analysis?
- Multi indication surrogacy models.
- Data generating mechanism for simulation study.
- Comparison of surrogate models to non-sharing models

Note we focus on surrogacy models here but this is one part of a larger simulation study.

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Background on oncology health technology assessment

- Technology appraisals in oncology often seek make decisions based on overall survival (OS), but increasingly cancer drugs are being licensed based on progression-free survival (PFS).
- Drugs may be approved in one indication (e.g. breast cancer) then have their license extended to additional indications as trial evidence accumulates over time (e.g. bladder cancer)
- Evidence synthesis methods which allow for sharing of information on effects across indications, could provide more precise treatment effect estimates on OS in the indication of interest i.e. “target indication”.

Background on multi-indication meta-analysis

- Standard hierarchical models [1] have been developed to pool data across indications but only allow for sharing of information on the effect for OS.
- Bivariate/surrogacy models, that have been developed for sharing of information on a surrogate relationship across treatment classes [2]. Singh et al (in press) extended to share across indications.
  - Can be used to predict the effect on OS in HTA.

Question: can multi-indication surrogacy models provide accurate and strengthened inferences compared to traditional HTA (non-sharing) methods?

[1] Hemming K, Bowater RJ, Lilford RJ. Pooling systematic reviews of systematic reviews: a Bayesian panoramic meta-analysis. Statistics in Medicine. 2012 Feb 10;31(3):201-16.

[2] Papanikos T, Thompson JR, Abrams KR, Städler N, Ciani O, Taylor R, Bujkiewicz S. Bayesian hierarchical meta-analytic methods for modeling surrogate relationships that vary across treatment classes using aggregate data. Statistics in medicine. 2020 Apr 15;39(8):1103-24.

Modelling a surrogate relationship between endpoints

- Data are assumed to be available for treatment effects on both a surrogate endpoint and a final clinical outcome (e.g., PFS and OS) from each study in an indication.
- Within-study model: The observed effects on the two outcomes in each study are assumed to follow a joint (bivariate) distribution to account for their correlation.

LHR PFS

LHR OS

$$\begin{pmatrix} Y_{1ij} \\ Y_{2ij} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1ij} \\ \delta_{2ij} \end{pmatrix}, \begin{pmatrix} \sigma^2_{1ij} & \sigma_{1ij}\sigma_{2ij}\rho_{wij} \\ \sigma_{1ij}\sigma_{2ij}\rho_{wij} & \sigma^2_{2ij} \end{pmatrix} \right)$$

- Between-studies model: The assumed linear surrogate relationship between the true effects on the surrogate endpoint and the final outcome from studies within an indication can be summarised by intercept, slope, and conditional variance parameters.

$$\delta_{2ij} \sim N\left(\gamma_{0j} + \gamma_{1j}\delta_{1ij}, \psi_j^2\right),$$

Simulation study

- Simulate outcomes in “non-target” (e.g. breast cancer, lung cancer) indications and a “target” indication (e.g. bladder cancer).
- Use models to predict the relative effect of treatment on OS in the target indication i.e. the log hazard ratio for overall survival (LHROS).

Data generating mechanism

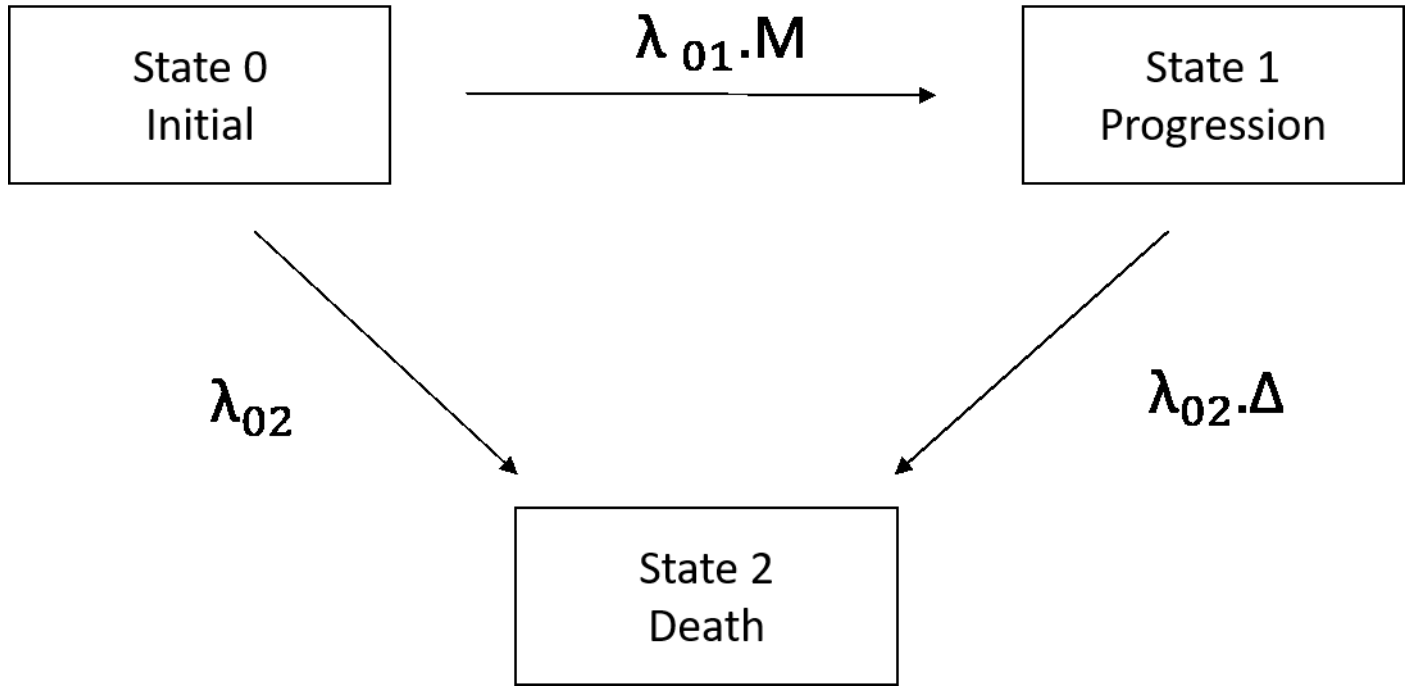
- 1) A multi-state model to jointly simulate underlying true hazard ratios (HRs) for PFS and OS
- 2) How parameters differ within- and between-indications
- 3) Size of dataset

1) Data generating mechanism: multi state model

- 3-state, multi-state model (MSM), common in oncology
- Exponential transitions
- Treatment effect on progression only

- PFS = time in initial (state 0)
- OS = time until death (state 2)

- Induces clinically plausible relationship between LHR PFS and OS
- Note that models mis-specified



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2) Data generating mechanism: parameters

- Which parameters to use in the multi-state model?
- Control arm parameters based on bevacizumab. Backfit to find parameters (λ_{01}, λ_{02}, Δ) consistent with observed PFS and OS values.
- Explore the impact of different treatment effects on progression (M).
  - Coefficient of variation (CV) = σ/μ.
  - CV = 0%, 7%, 15%, 30% and 50% within and between indications
- Explore impact of “outlier” indications
  - Severe outlier => one indication has mean M 6 SD from overall mean
  - Target outliers => the target indication has mean M 1.96 SD from overall mean

3) Data generating mechanism: dataset

Large dataset: 7 indications with 9, 8, 6, 3, 2, 1, 1 studies.

Small dataset: 3 indications with 3, 2, 1 studies.

Target indication always has one study, reporting PFS and OS.

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Models

Univariate model (traditional HTA)

- Estimate LHR OS from the single study in the target indication (j*).

$$Y_2 \sim N(\delta_2, \sigma_2^2)$$
$$\delta_2 \sim N(d_2, \tau_2)$$

- Treatment effect in target indication given flat prior d_{2j*} ~ N(0, 10^2). No sharing across indications.
- Within indication heterogeneity (τ_2) given weakly informative half normal prior distributionτ_2 ~ |N (0, 0.5^2)| and allow to share information across indications (Rover et al, 2021).

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Models

Surrogacy model

1. Estimate the relationship between LHR PFS and OS in non-target indications (assume common surrogacy parameters across indications)

$$\begin{pmatrix} Y_{1ij} \\ Y_{2ij} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1ij} \\ \delta_{2ij} \end{pmatrix}, \begin{pmatrix} \sigma_{1ij}^2 & \sigma_{1ij}\sigma_{2ij}\rho_{wij} \\ \sigma_{1ij}\sigma_{2ij}\rho_{wij} & \sigma_{2ij}^2 \end{pmatrix} \right)$$

$$\delta_{2ij} \sim N\left(\gamma_{0j} + \gamma_{1j}\delta_{1ij}, \psi_j^2\right),$$

2. Estimate LHR PFS from single target indication study (same model as for OS): $\delta_1 \sim N(d_1, \tau_1)$
3. Predict LHR OS in target indication.

$$\gamma_0 + \gamma_1 d_1$$

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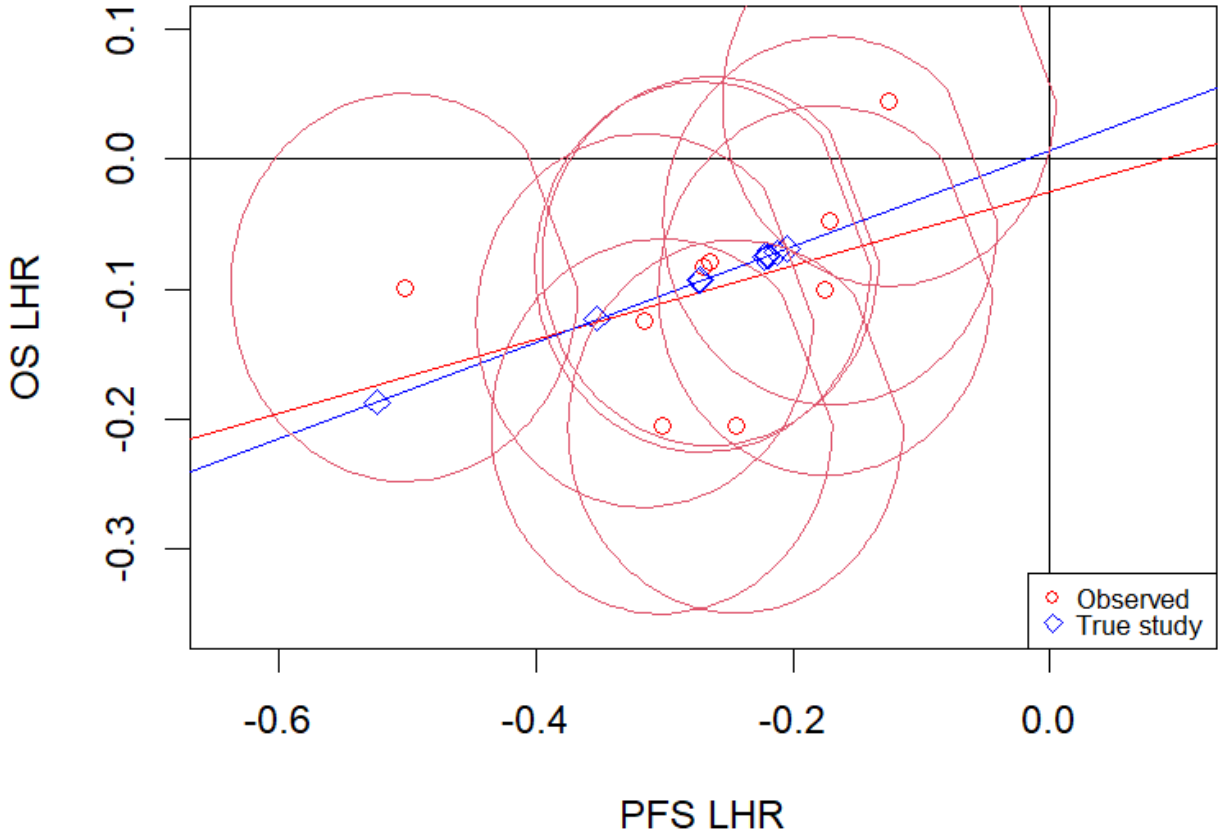
Surrogate models

- Surrogacy within a single indication (9 studies), iteration 1
- PFS LHR x-axis, OS LHR y-axis
- Shallow slope => large changes in LHR PFS associated with small changes in LHR OS



- Blue dots are “true study effects” (without sampling uncertainty). Spread out as there is between study (within indication) heterogeneity. Bule line is the “true surrogacy line”
- Red dots/line are the observed study effects and regression line.

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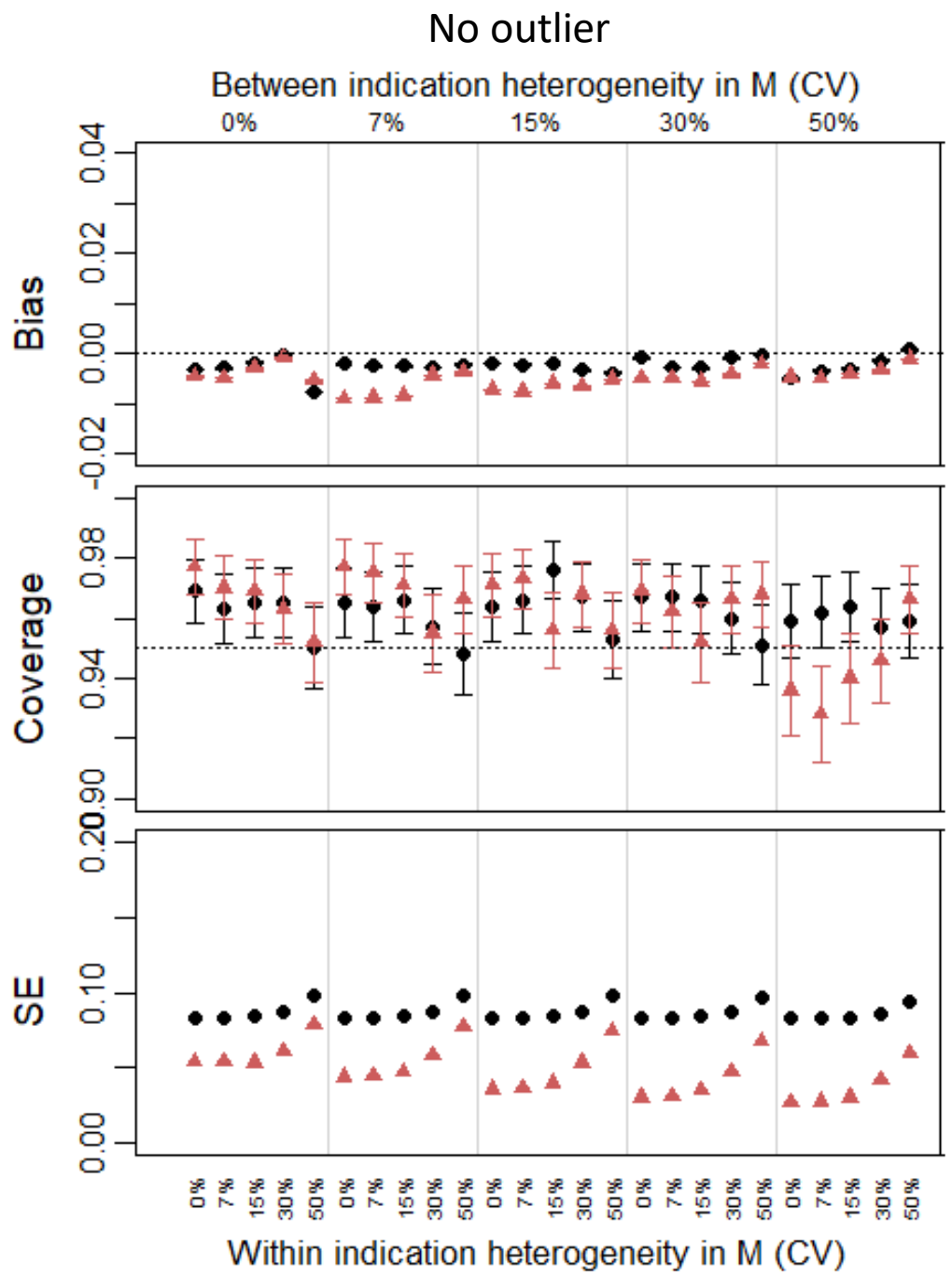


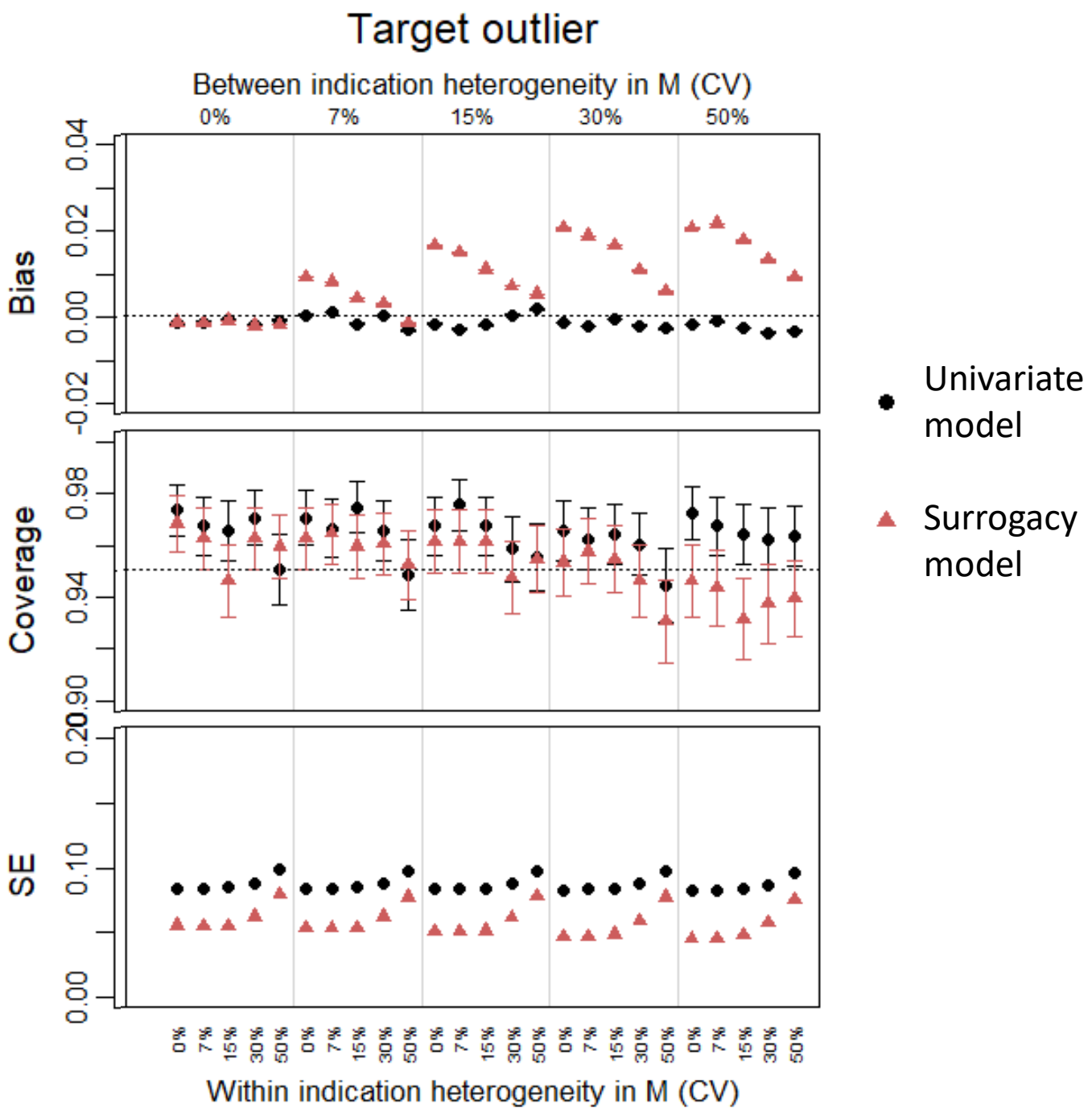
Univariate model

Surrogacy model

Large dataset

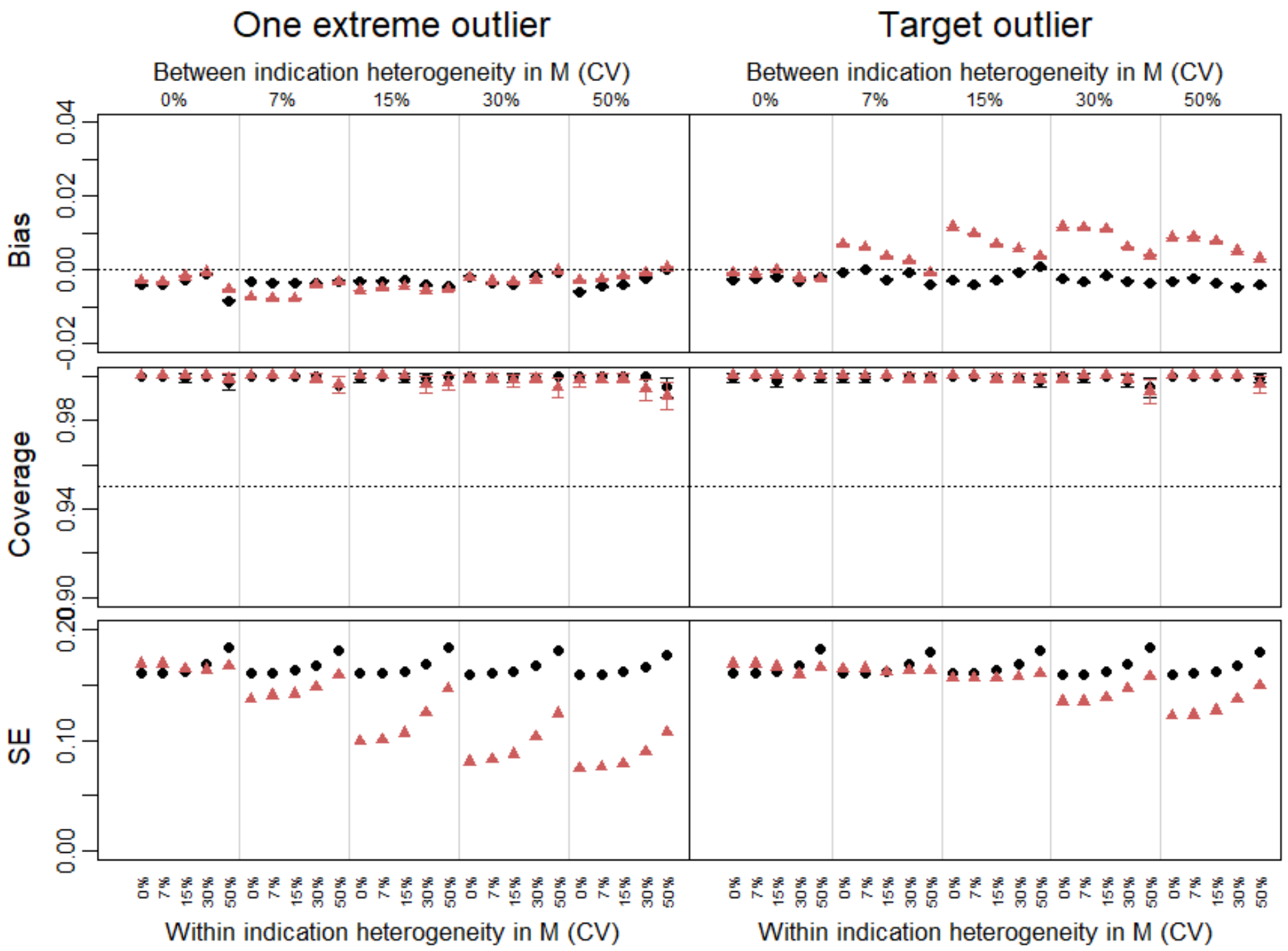
- No outlier
- Within and between indication heterogeneity
- Bias, low
- 95% coverage, OK
- Lower SE with surrogacy because more PFS events than OS events.
- SE increases with higher within indication heterogeneity

- Results are very similar when one extreme outlier => surrogacy can handle this case.



Large dataset

- Target indication is an outlier
- Coverage and SE very similar to previous
- Univariate model always has low bias – based on one unbiased OS study
- Surrogacy model requires within indication heterogeneity to estimate surrogacy relationship.



Univariate model

Surrogacy model

Small dataset

- Bias similar to large dataset
- Underconfident coverage (better prior required?)
- Surrogacy reduces uncertainty with more between indication heterogeneity?

Discussion and conclusions

- Question: can multi-indication surrogacy models provide accurate and strengthened inferences compared to non-sharing methods?
- Answer: somewhat, but only under certain conditions!
  - Can offer modest reductions in uncertainty
  - Require high within indication heterogeneity in treatment effect (M) to remove bias
- Additional simulations show that heterogeneity in other parameters e.g. mortality increase post progression (Δ) result in a non-linear or non-existent surrogacy relationship!
  - Further research required to understand the clinical judgements required for valid application of surrogacy models.
- Full simulation study looks at a wide range of multi-indication models and evidence sets

Additional slides

Models x18

Univariate non-mixture (x6):

- IE, CE, RE with and without common heterogeneity within indications

Univariate mixture (x4):

- MCIE, MRIE with and without common heterogeneity within indications

Surrogate (x8)

"Unmatched" uses IE for PFS estimate

- CE surrogate and IE PFS (independent hetero)
- CE surrogate and IE PFS (common hetero)
- RE surrogate and IE PFS (independent hetero)
- RE surrogate and IE PFS (common hetero hetero)

"Matched" uses the same assumption for surrogacy and PFS estimate

- CE surrogate and CE PFS (independent hetero)
- CE surrogate and CE PFS (common hetero)
- RE surrogate and RE PFS (independent hetero)
- RE surrogate and RE PFS (common hetero)

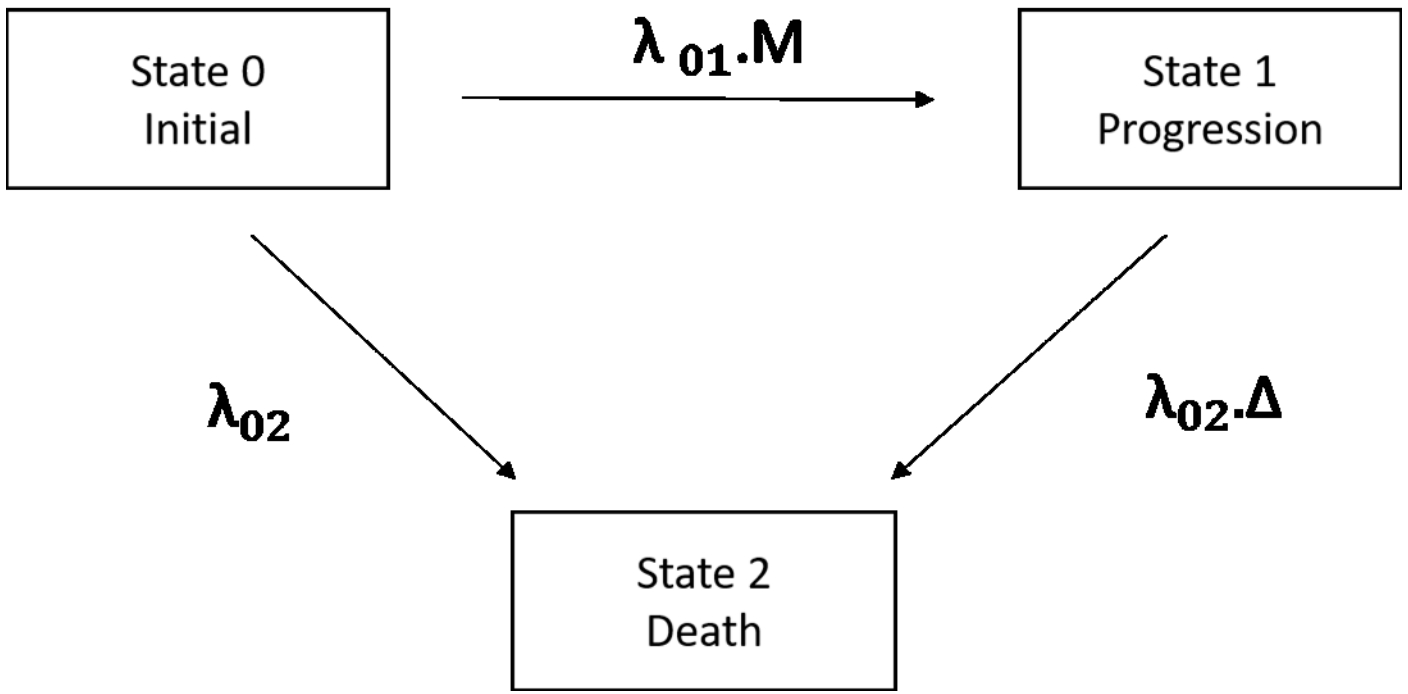
Data generating mechanism: overview

$CV = \sigma/\mu$

Within indication heterogeneity (CV)	Between indication heterogeneity (CV)	Evidence base	Overall survival data in target indication	Outlier indication
0%	0%	Small (3 indications)	Yes	None
7%	7%	Medium (5 indications)	No	One (moderate)
15%	15%	Large (7 indications)		One (extreme)
30%	30%			All (moderate)
50%	50%			

- The full set of design factors factorially varied in the simulation study above. This results in (5 x 5 x 3 x 2 x 4 =) 600 simulation scenarios
- For each scenario 1000 datasets are simulated

Multi state models and feasible surrogacy



As shown in Erdmann et al (2023), the underlying values of HR OS and HR PFS (without sampling uncertainty) can be written as a function of the MSM parameters and duration of follow-up (t). The log HR for PFS is given by:

$$\text{LHR PFS} \quad = ln\left(\frac{\lambda_{01}.M + \lambda_{02}}{\lambda_{01} + \lambda_{02}}\right). \qquad (1)$$

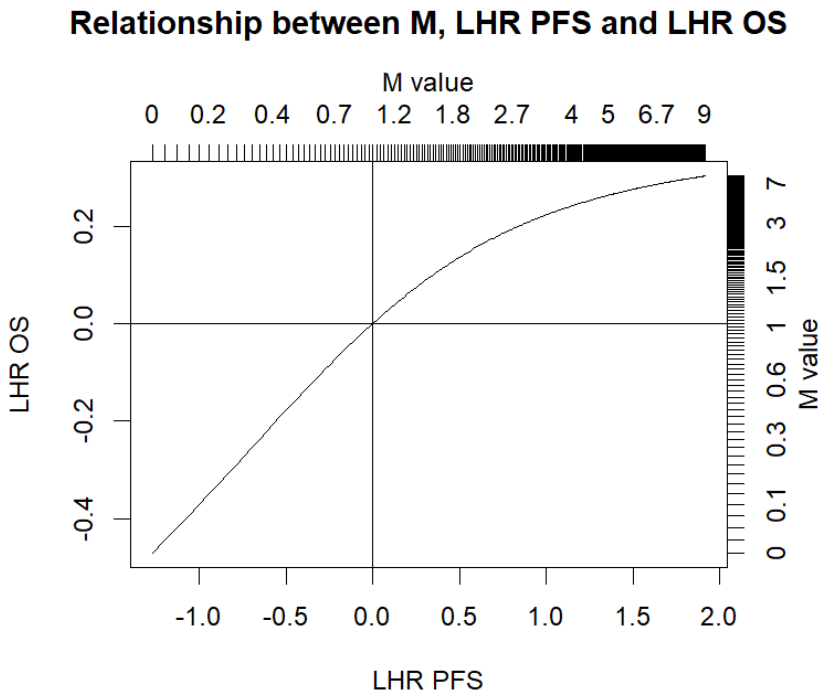
The OS hazard (h) in the control and treatment groups are below:

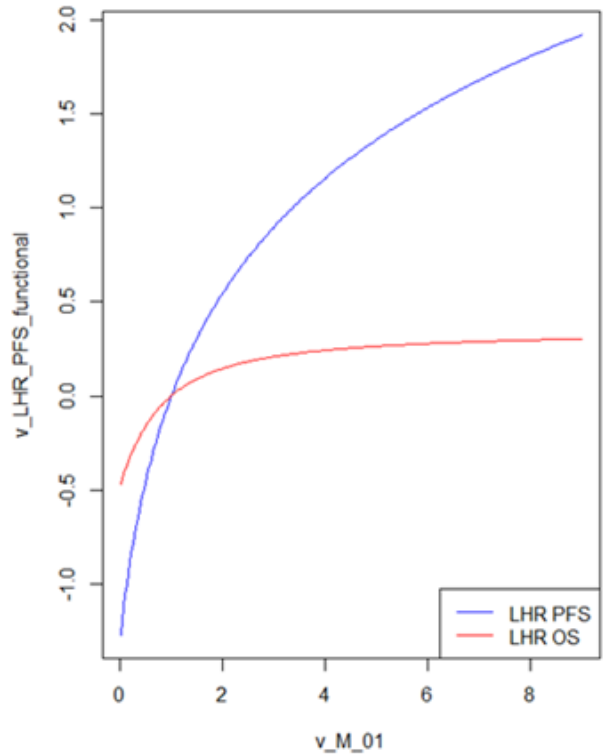
$$h_{OS,ctrl} = \frac{\Delta(\lambda_{01} + \lambda_{02}) - \lambda_{01}.\lambda_{02} + \Delta.exp((\lambda_{01} - \Delta).t)}{\Delta - \lambda_{01}.exp((\lambda_{01} - \Delta).t)},$$

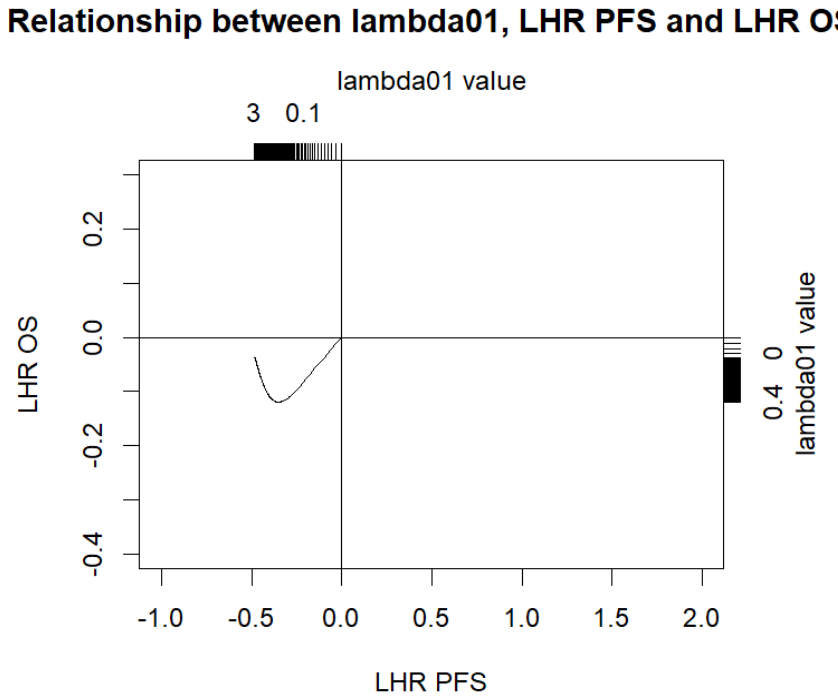
$$h_{OS,trt} = \frac{\Delta(\lambda_{01}.M + \lambda_{02}) - \lambda_{01}.M.\lambda_{02} + \Delta.exp((\lambda_{01}.M - \Delta).t)}{\Delta - \lambda_{01}.M.exp((\lambda_{01}.M - \Delta).t)}.$$

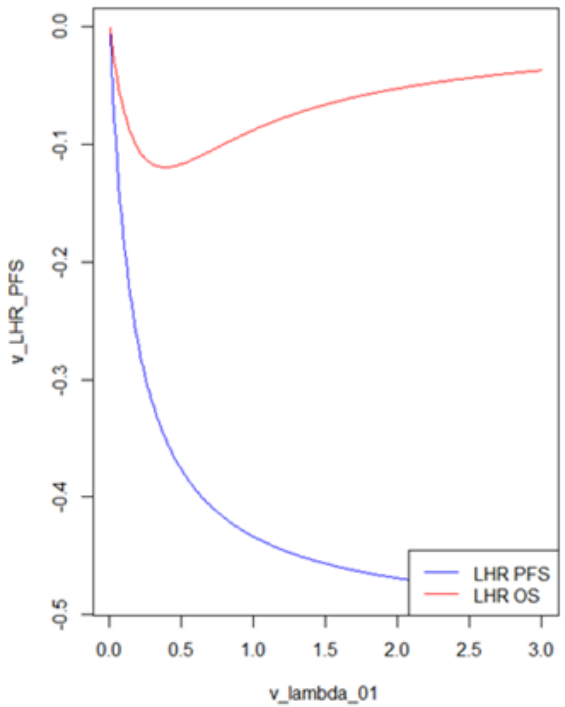
Therefore, the LHR OS is the log of the ratio of these hazards.

$$\text{LHR OS} = \ ln\left(\frac{h_{OS,trt}}{h_{OS,ctrl}}\right). \qquad (2)$$

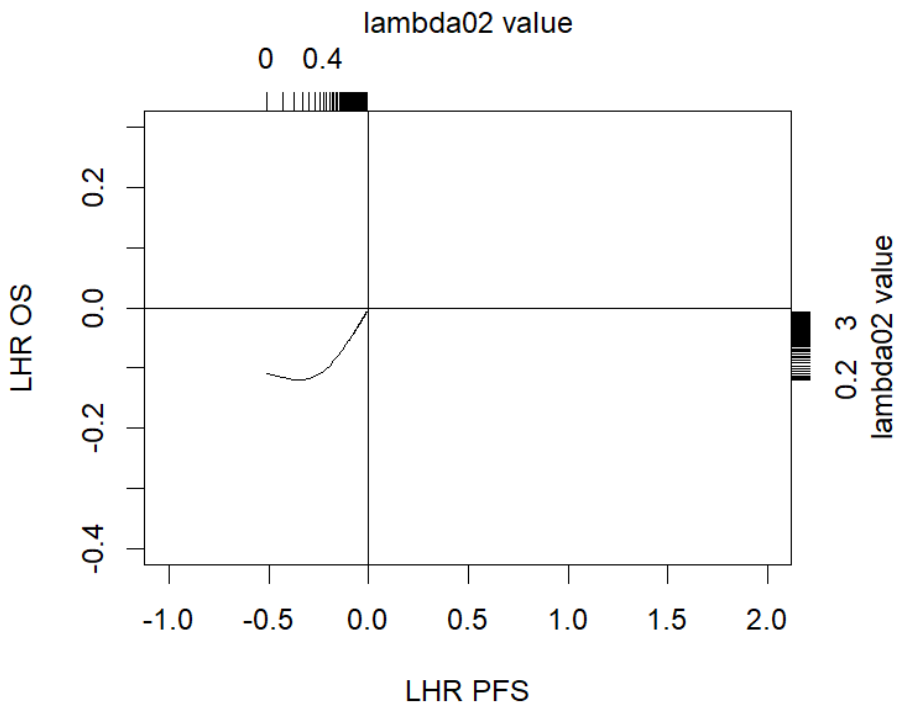

Relationship between M, LHR PFS and LHR OS
M value
0 0.2 0.4 0.7 1.2 1.8 2.7 4 5 6.7 9
LHR OS
0.2
0.0
-0.2
-0.4
M value
0 0.1 0.3 0.6 1 1.5 3 7
-1.0 -0.5 0.0 0.5 1.0 1.5 2.0
LHR PFS

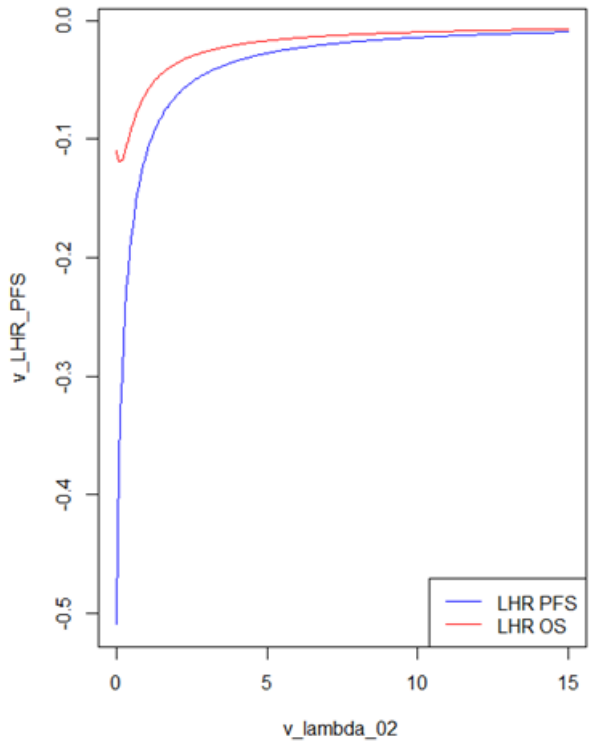

v_LHR_PFS_functional
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
LHR PFS
LHR OS
0 2 4 6 8
v_M_01

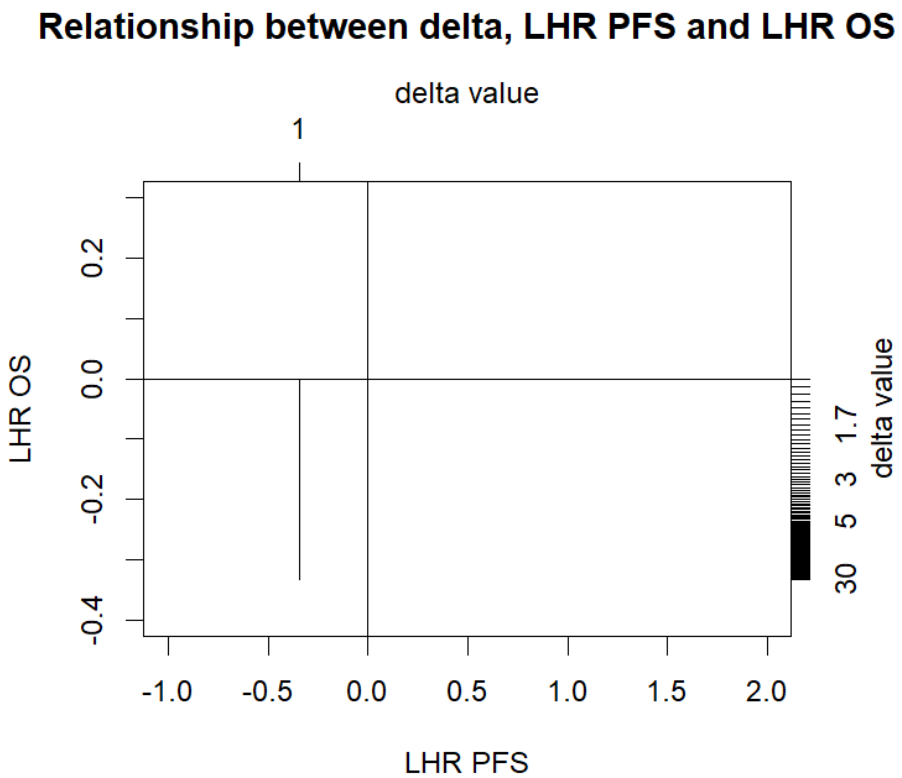

Relationship between lambda01, LHR PFS and LHR OS
lambda01 value
3
0.1
LHR OS
0.2
0.0
-0.2
-0.4
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
LHR PFS
0.4
0
lambda01 value

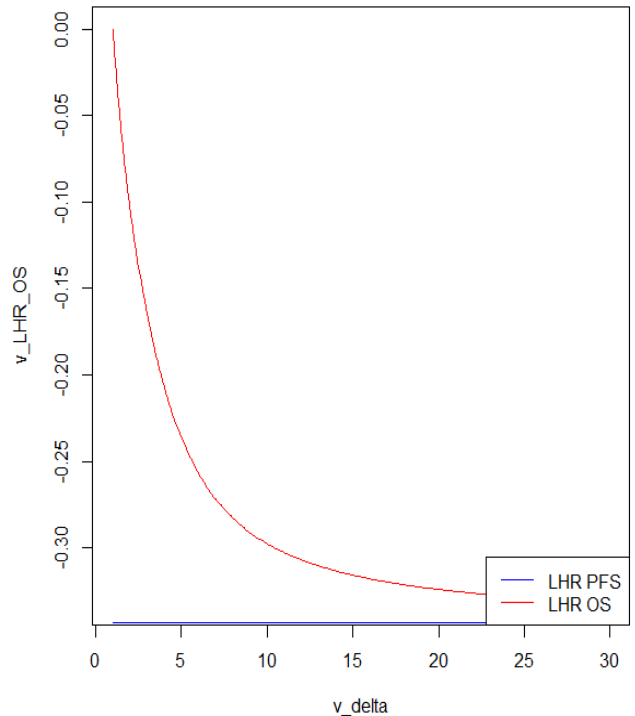

v_LHR_PFS
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
v_lambda_01
LHR PFS
LHR OS

Relationship between lambda02, LHR PFS and LHR OS






Relationship between delta, LHR PFS and LHR OS
delta value
1
LHR OS
0.2
0.0
-0.2
-0.4
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
LHR PFS
1.7
3
5
30
delta value


v_LHR_OS
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
-0.30
0
5
10
15
20
25
30
v_delta
LHR PFS
LHR OS