

Supplementary Appendix 3

NCPE

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1 Importance sampling: model diagnostics, parameter distributions, and survival estimates

The tables and figures in this section show survival curve parameter estimates, covariance structures, importance sampling diagnostics, and (probabilistic) survival curve predictions, obtained from trial data only estimated using maximum likelihood estimation (MLE), and combining trial data with external information using the importance sampling algorithm described in the methods section of the main article and in Appendix 1.

Table 1: Parameter estimates obtained using trial data only (left) and combining trial data with external information (right): Exponential distribution.

x	x
-4.562874	-4.467088

Table 2: Covariance matrices obtained using trial data only (left) and combining trial data with external information (right): Exponential distribution.

0.0138444		rate
	rate	0.0169491

Diagnostics – exponential

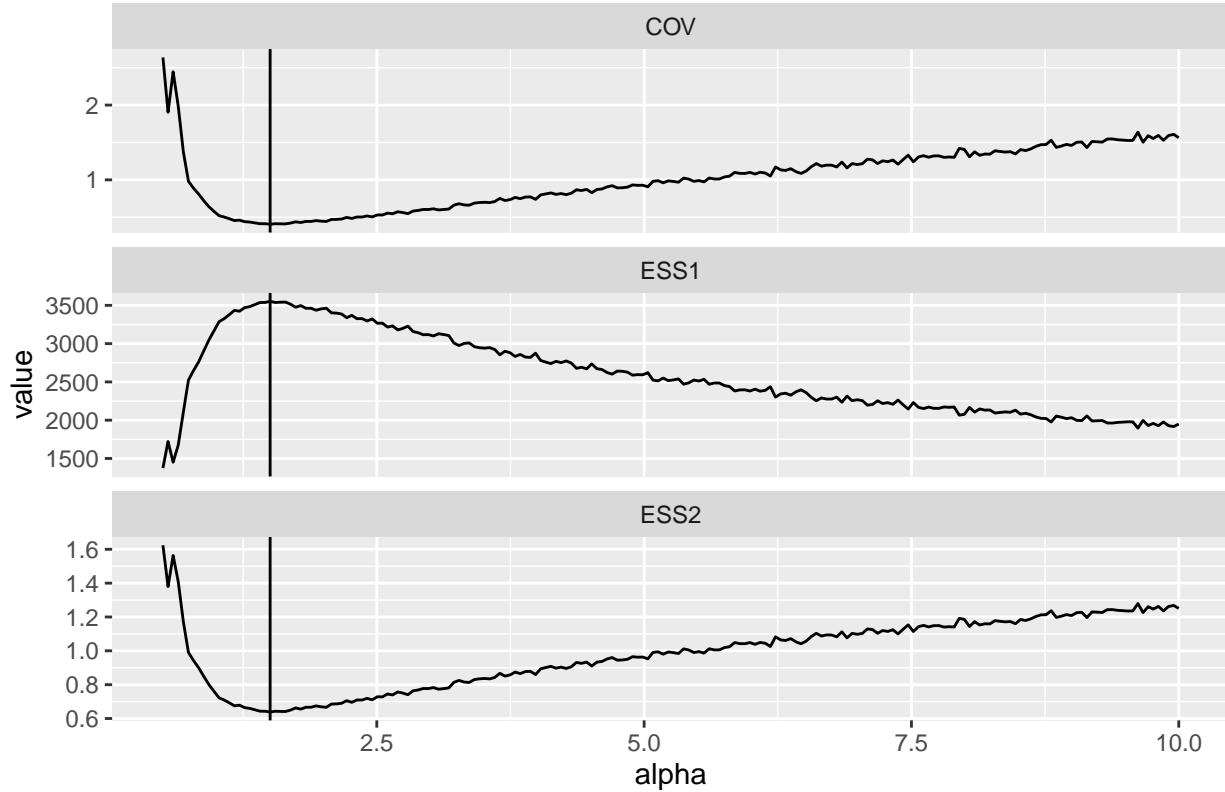


Figure 1: Importance sampling diagnostics: coefficient of variation (COV) and effective sample size (ESS) as functions of the tempering parameter alpha, Exponential distribution. The vertical line shows the optimal value of alpha identified by the algorithm.

Parameters – exponential

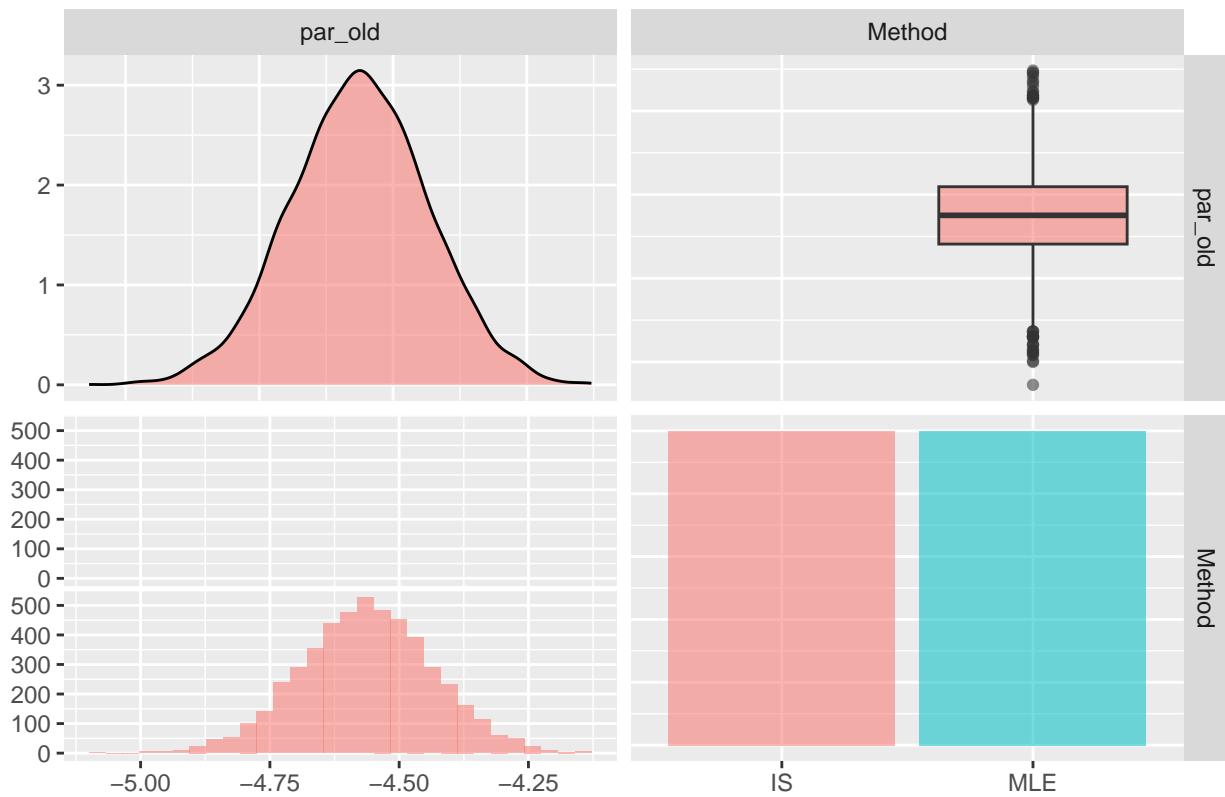


Figure 2: Survival curve parameter distributions and covariance estimates obtained using trial data only (MLE) and combining trial data with external information (IS), Exponential distribution

Survival – exponential

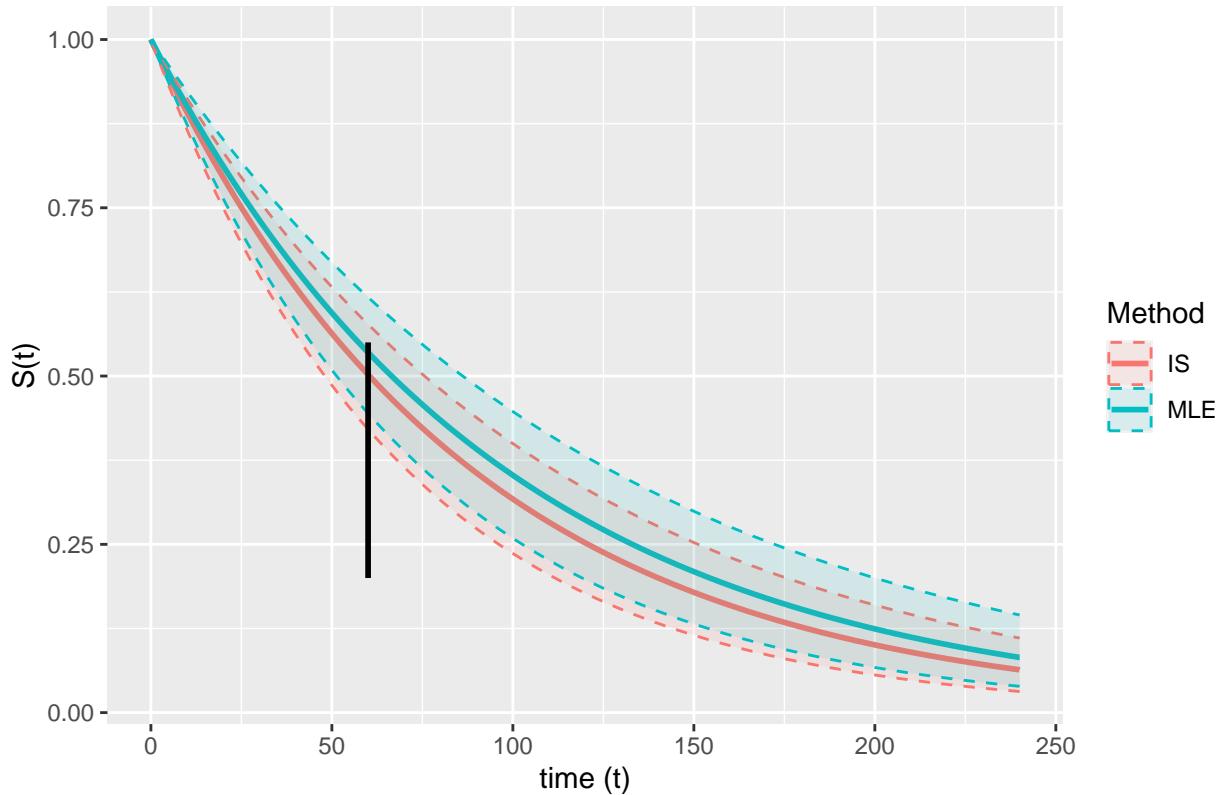


Figure 3: Survival curves (median and 95% confidence intervals) obtained using trial data only (MLE) and combining trial data with external information (IS), Exponential distribution

Table 3: Parameter estimates obtained using trial data only (left) and combining trial data with external information (right): Weibull distribution.

	x		x
shape	0.2028128	shape	0.2199019
scale	4.2127617	scale	4.1750757

Table 4: Covariance matrices obtained using trial data only (left) and combining trial data with external information (right): Weibull distribution.

	shape	scale		shape	scale
shape	0.0094518	-0.0118402	shape	0.0147844	-0.0228526
scale	-0.0118402	0.0235769	scale	-0.0228526	0.0466213

Diagnostics – weibull

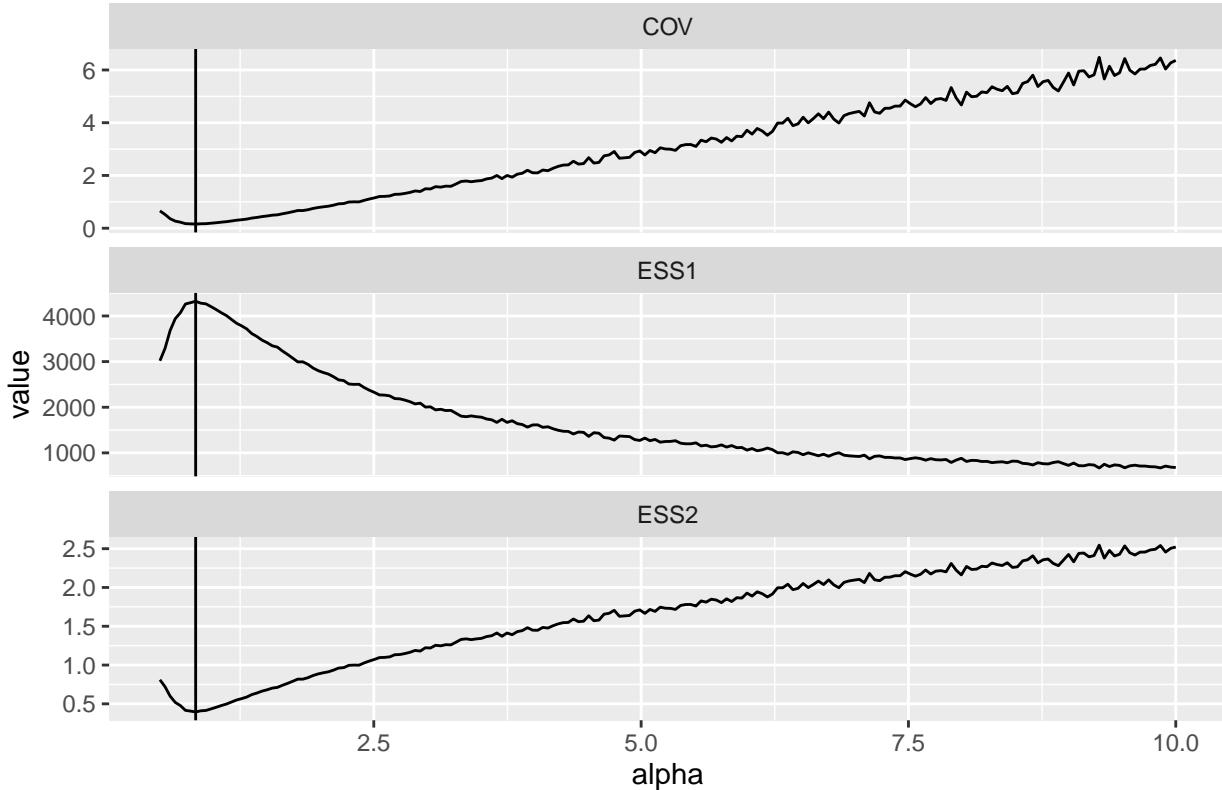


Figure 4: Importance sampling diagnostics: coefficient of variation (COV) and effective sample size (ESS) as functions of the tempering parameter alpha, Weibull distribution. The vertical line shows the optimal value of alpha identified by the algorithm.

Parameters – weibull

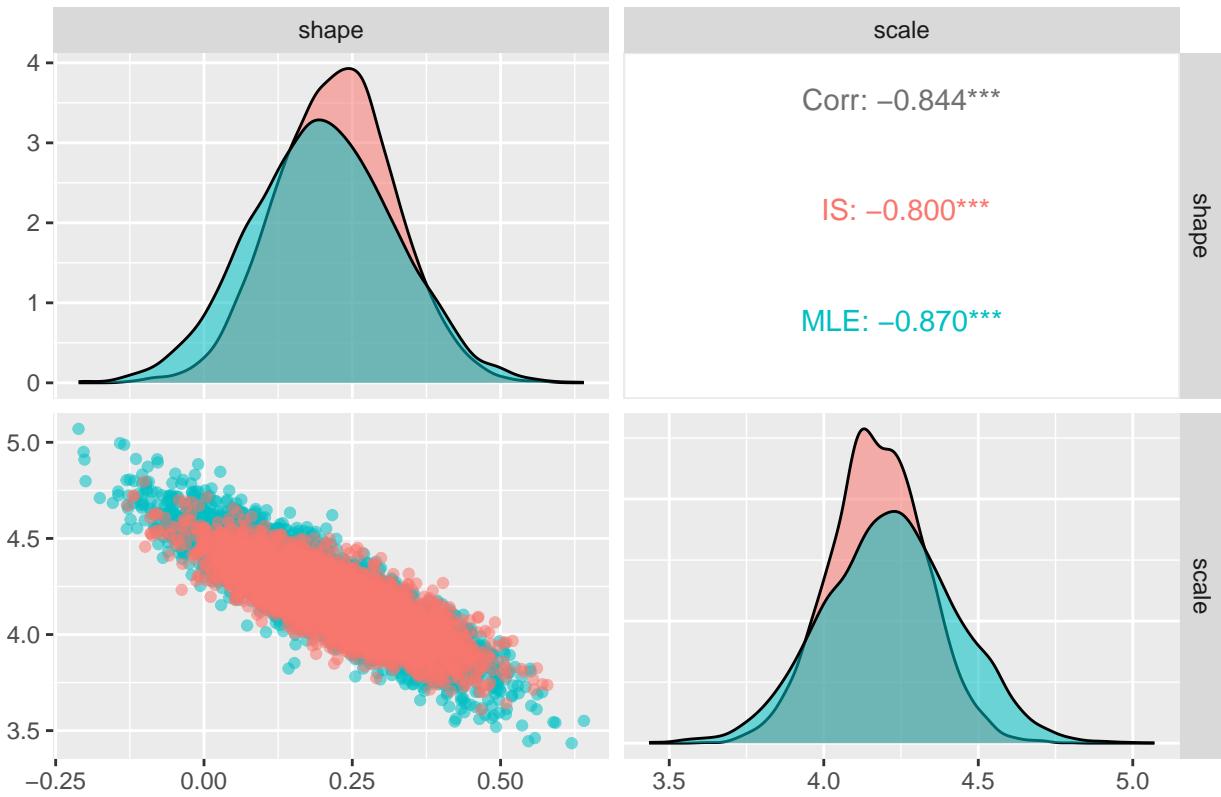


Figure 5: Survival curve parameter distributions and covariance estimates obtained using trial data only (MLE) and combining trial data with external information (IS), Weibull distribution

Survival – weibull

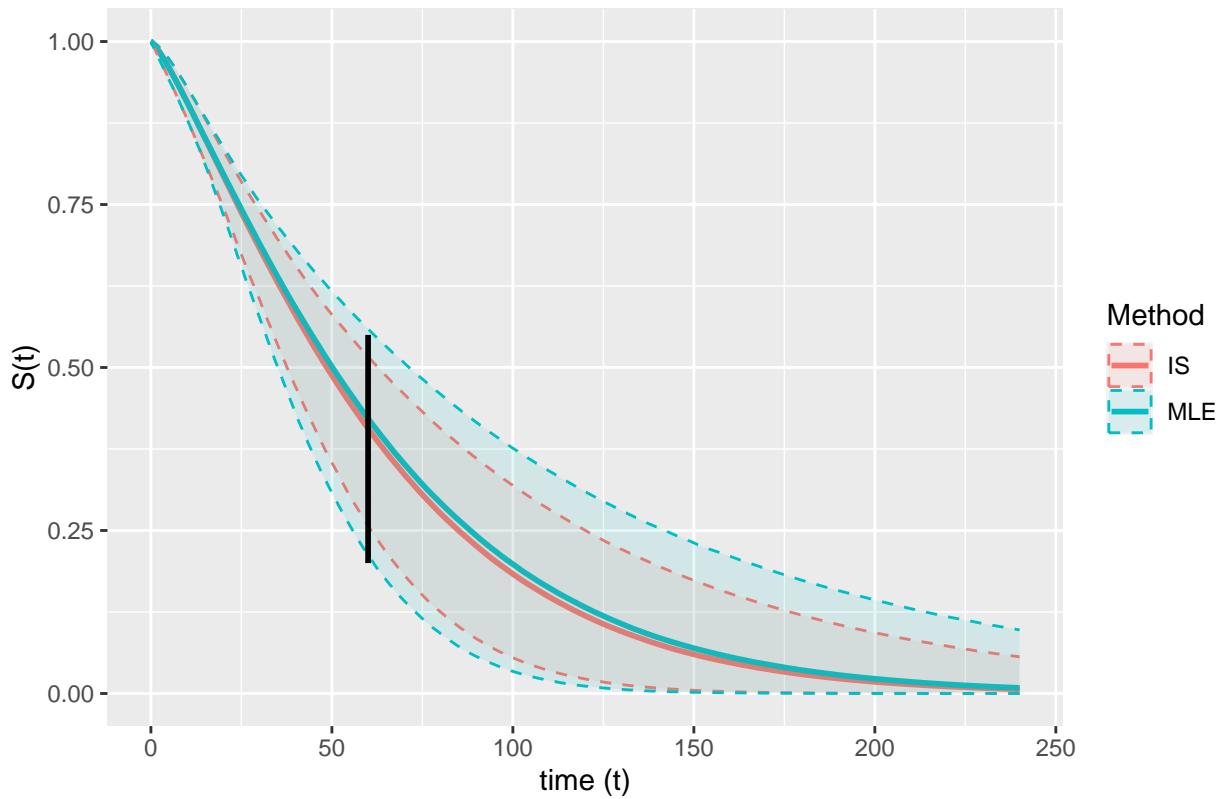


Figure 6: Survival curves (median and 95% confidence intervals) obtained using trial data only (MLE) and combining trial data with external information (IS), Weibull distribution

Table 5: Parameter estimates obtained using trial data only (left) and combining trial data with external information (right): Gompertz distribution.

	x		x
shape	0.0389625	shape	0.0197027
rate	-4.8682858	rate	-4.7220927

Table 6: Covariance matrices obtained using trial data only (left) and combining trial data with external information (right): Gompertz distribution.

	shape	rate		shape	rate
shape	0.0000970	-0.0013281	shape	0.0006747	-0.0056125
rate	-0.0013281	0.0316264	rate	-0.0056125	0.0636359

Diagnostics – gompertz

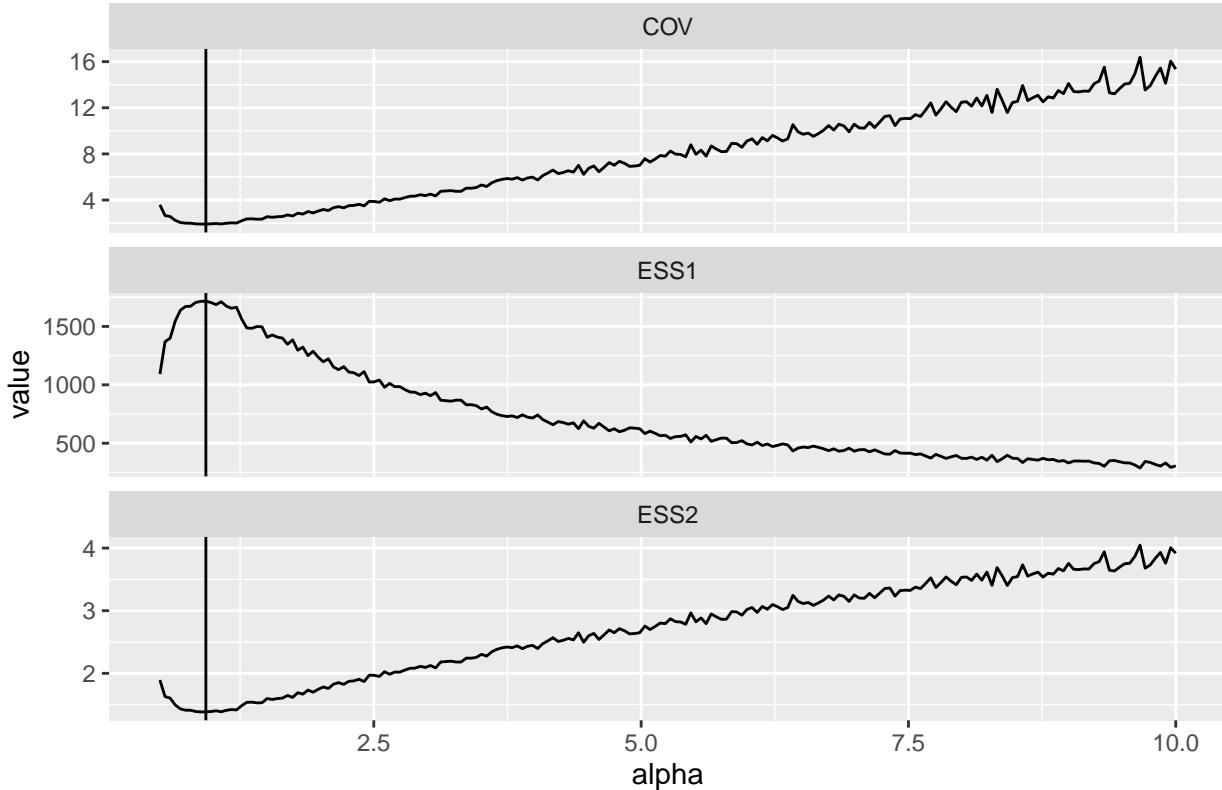


Figure 7: Importance sampling diagnostics: coefficient of variation (COV) and effective sample size (ESS) as functions of the tempering parameter α , Log-normal distribution. The vertical line shows the optimal value of α identified by the algorithm.

Parameters – gompertz

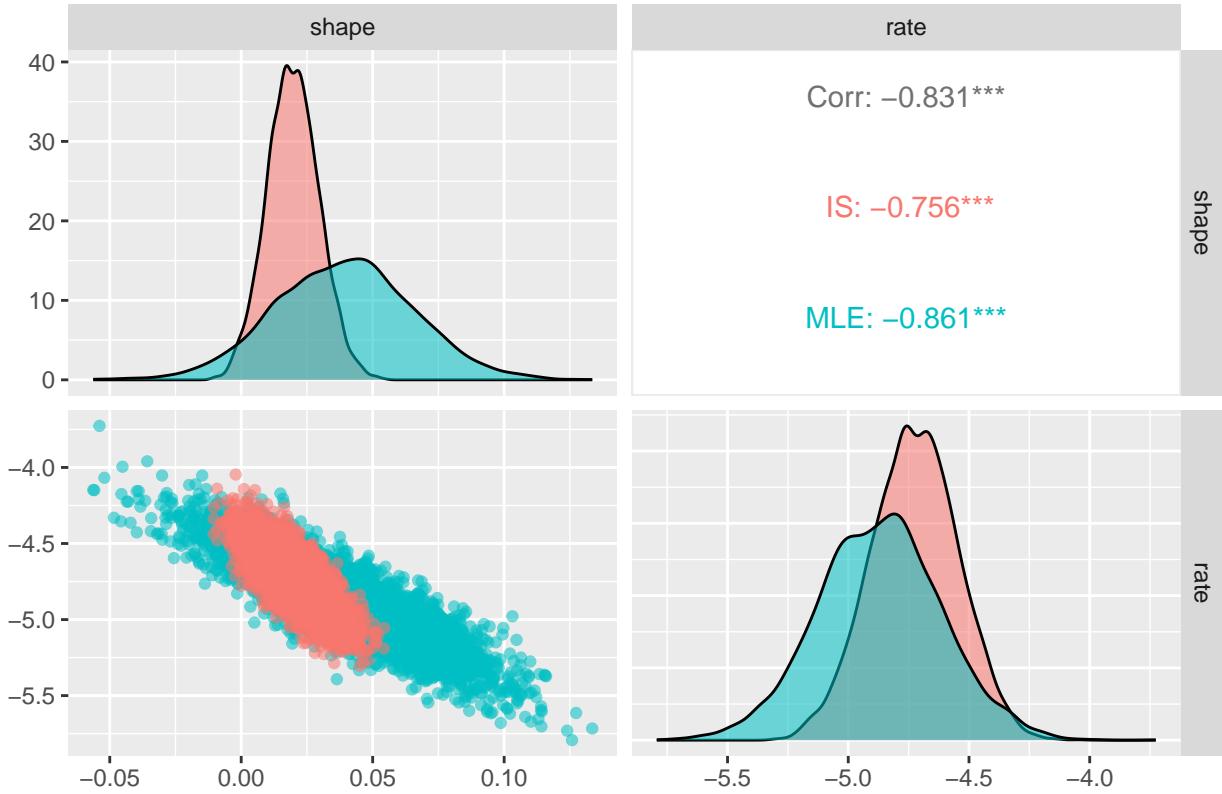


Figure 8: Survival curve parameter distributions and covariance estimates obtained using trial data only (MLE) and combining trial data with external information (IS), Log-normal distribution

Survival – gompertz

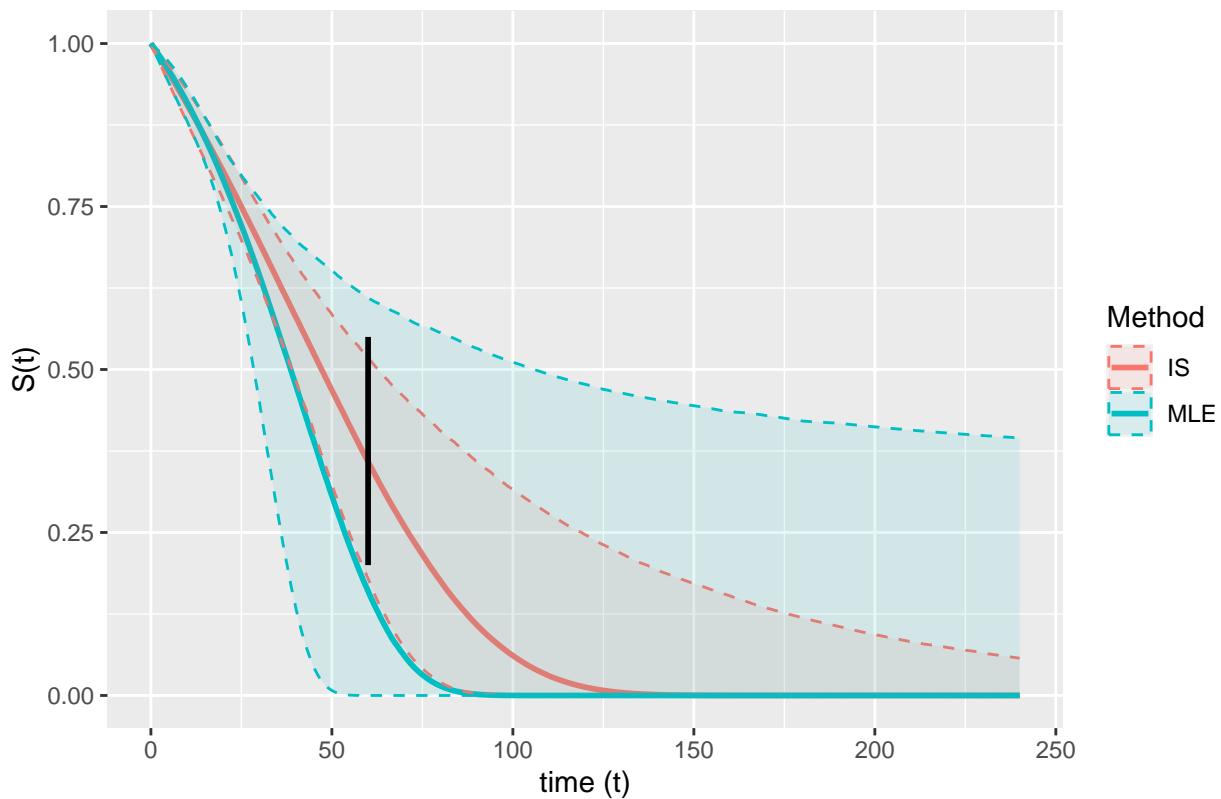


Figure 9: Survival curves (median and 95% confidence intervals) obtained using trial data only (MLE) and combining trial data with external information (IS), Log-normal distribution

Table 7: Parameter estimates obtained using trial data only (left) and combining trial data with external information (right): Log-normal distribution.

	x	x
meanlog	4.5379239	4.2299230
sdlog	0.5475716	0.4404943

Table 8: Covariance matrices obtained using trial data only (left) and combining trial data with external information (right): Log-normal distribution.

	meanlog	sdlog		meanlog	sdlog
meanlog	0.0545435	0.0201378	meanlog	0.0696811	0.0247171
sdlog	0.0201378	0.0100655	sdlog	0.0247171	0.0114622

Diagnostics – lognormal

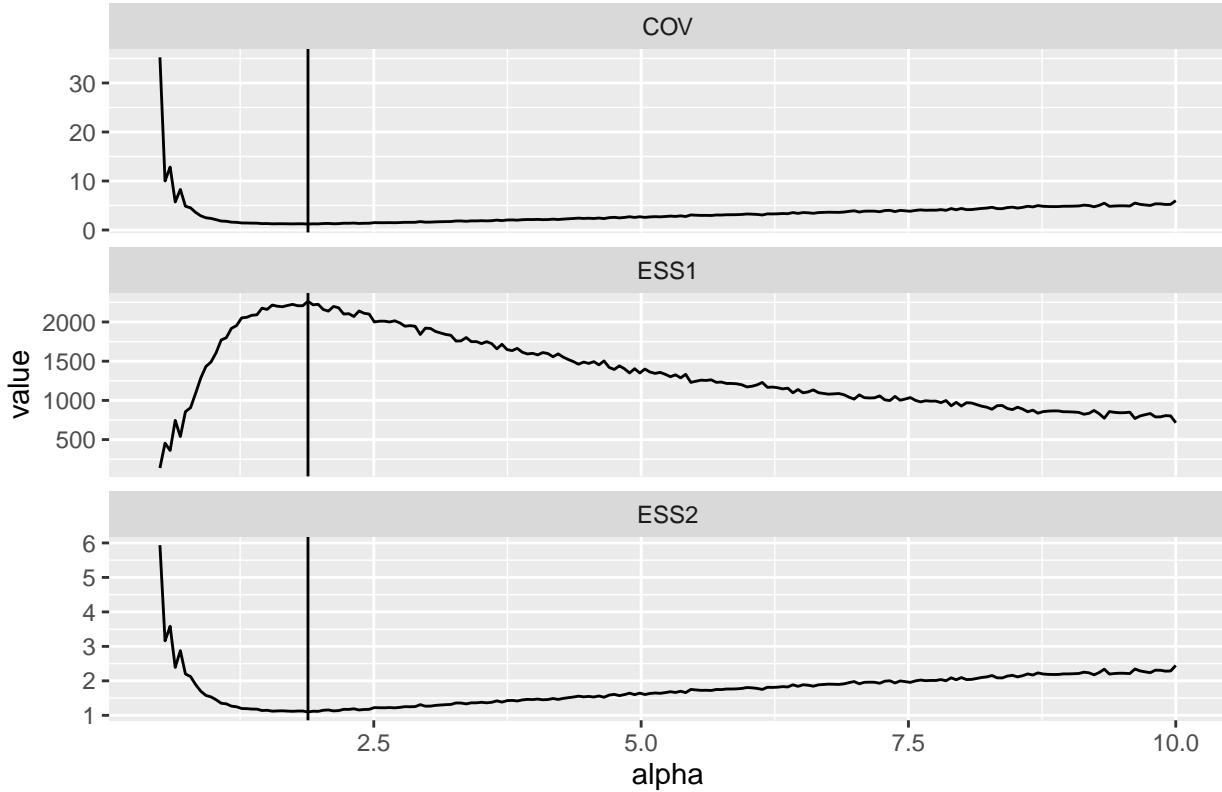


Figure 10: Importance sampling diagnostics: coefficient of variation (COV) and effective sample size (ESS) as functions of the tempering parameter alpha, Log-logistic distribution. The vertical line shows the optimal value of alpha identified by the algorithm.

Parameters – lognormal

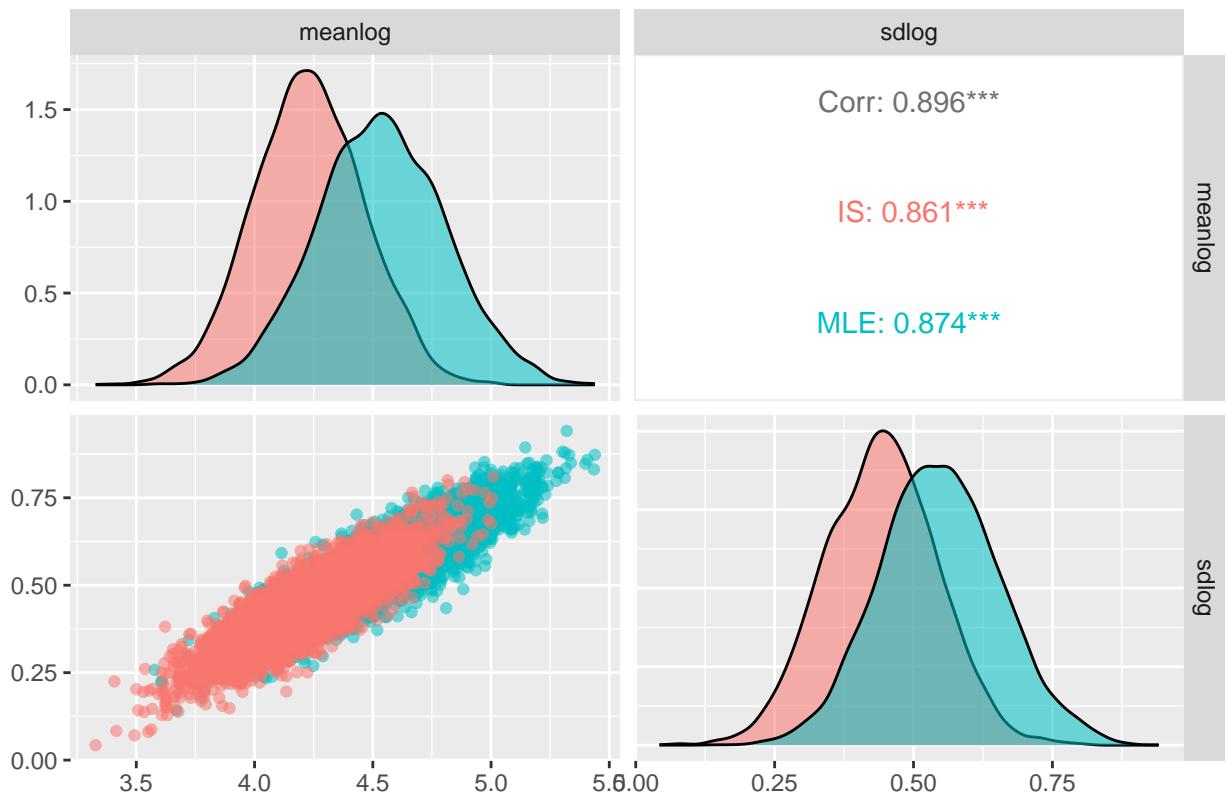


Figure 11: Survival curve parameter distributions and covariance estimates obtained using trial data only (MLE) and combining trial data with external information (IS), Log-logistic distribution

Survival – lognormal

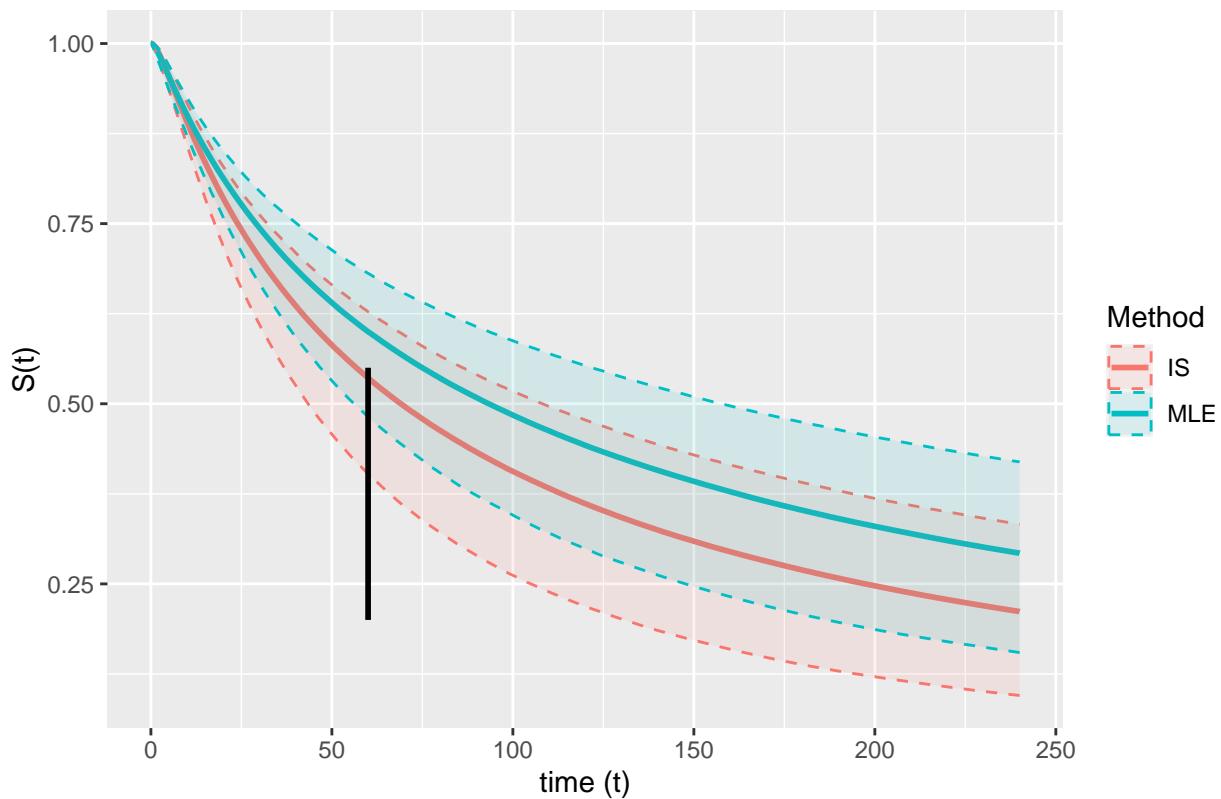


Figure 12: Survival curves (median and 95% confidence intervals) obtained using trial data only (MLE) and combining trial data with external information (IS), Log-logistic distribution

Table 9: Parameter estimates obtained using trial data only (left) and combining trial data with external information (right): Log-logistic distribution.

	x		x
shape	0.2450539	shape	0.3103417
scale	4.0866467	scale	3.9558382

Table 10: Covariance matrices obtained using trial data only (left) and combining trial data with external information (right): Log-logistic distribution.

	shape	scale		shape	scale
shape	0.0111243	-0.0139385	shape	0.0144928	-0.0213001
scale	-0.0139385	0.0276608	scale	-0.0213001	0.0434079

Diagnostics – llogis

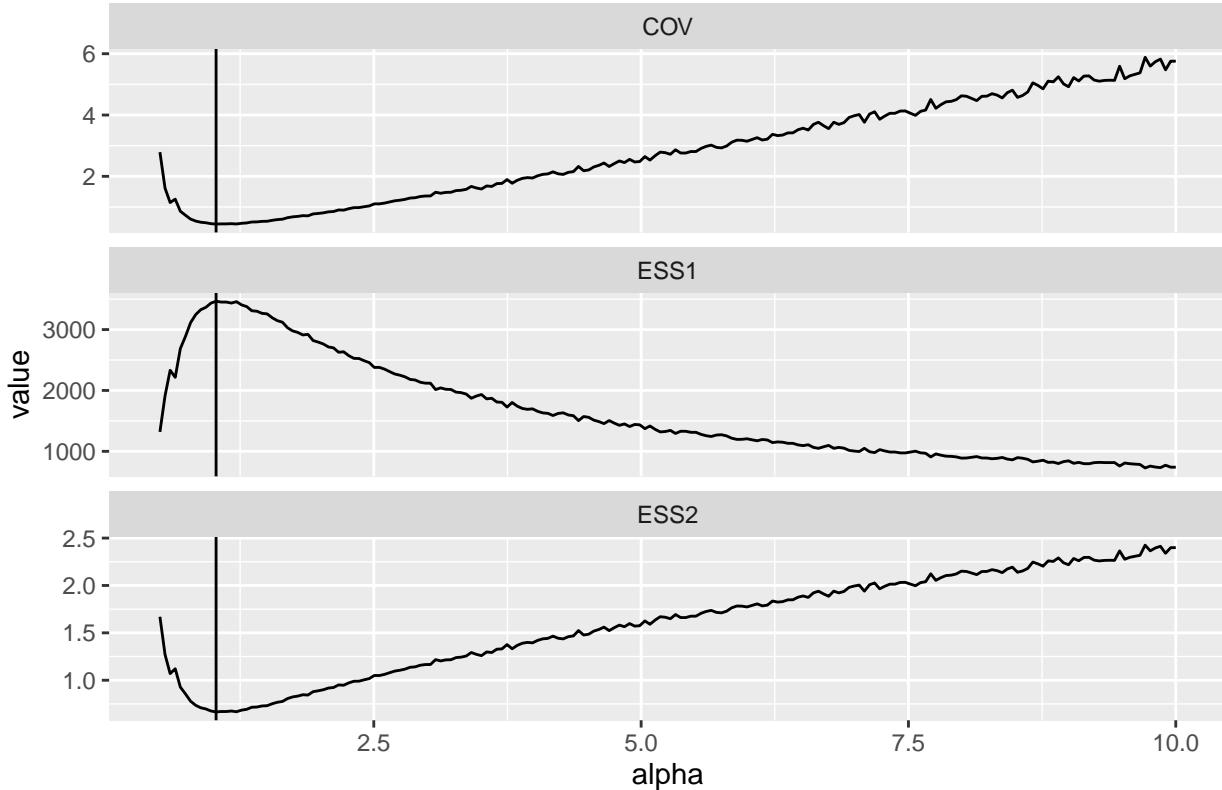


Figure 13: Importance sampling diagnostics: coefficient of variation (COV) and effective sample size (ESS) as functions of the tempering parameter alpha, Gompertz distribution. The vertical line shows the optimal value of alpha identified by the algorithm.

Parameters – llogis

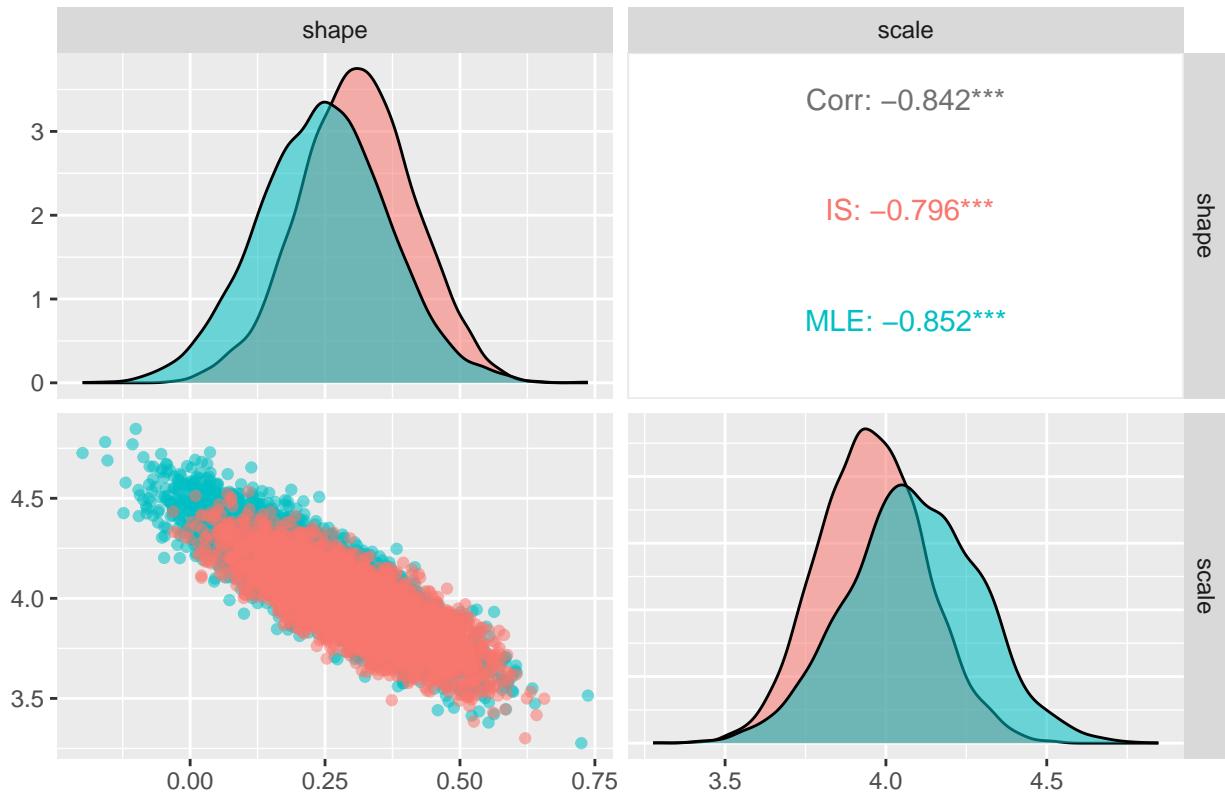


Figure 14: Survival curve parameter distributions and covariance estimates obtained using trial data only (MLE) and combining trial data with external information (IS), Gompertz distribution

Survival – Ilogis

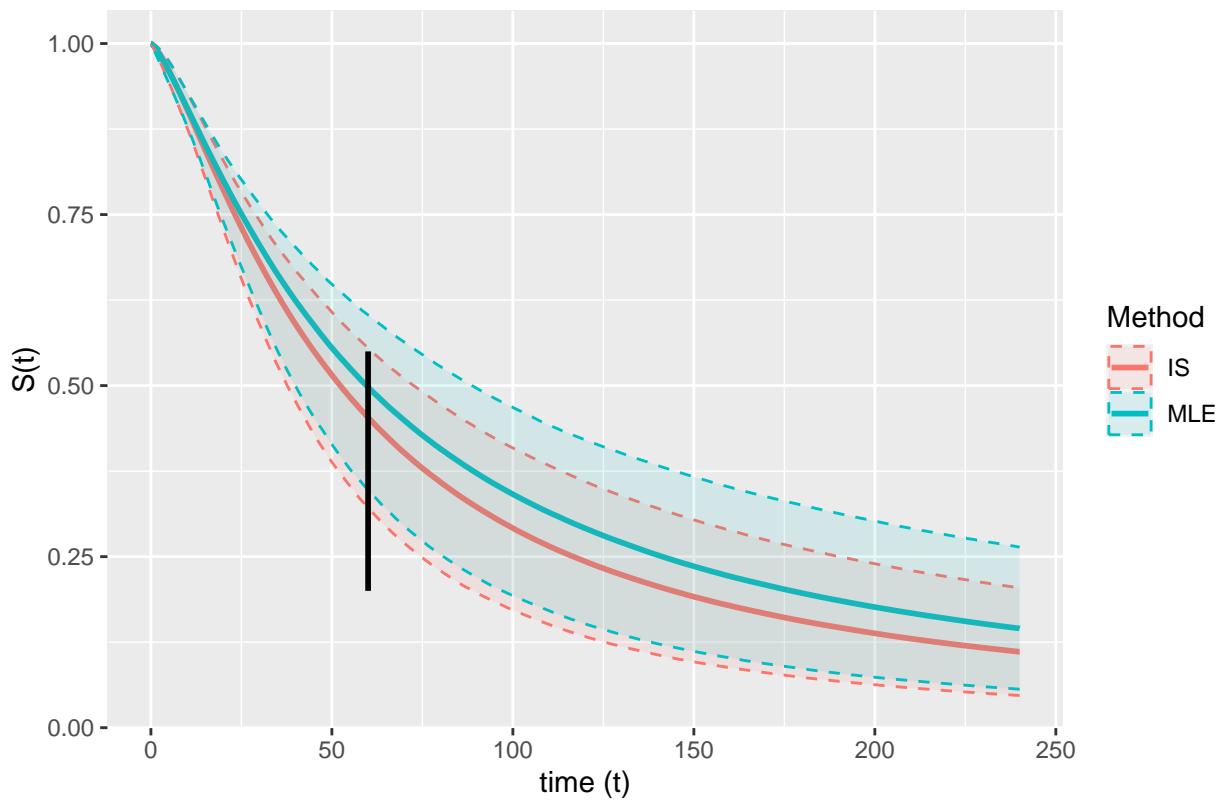


Figure 15: Survival curves (median and 95% confidence intervals) obtained using trial data only (MLE) and combining trial data with external information (IS), Gompertz distribution

Table 11: Parameter estimates obtained using trial data only (left) and combining trial data with external information (right): Gen. Gamma distribution.

	x	x	
mu	4.1703317	mu	4.1857610
sigma	-0.3599072	sigma	-0.3818327
Q	1.2031485	Q	1.2508022

Table 12: Covariance matrices obtained using trial data only (left) and combining trial data with external information (right): Gen. Gamma distribution.

	mu	sigma	Q		mu	sigma	Q
mu	0.0219135	0.0031467	0.0125013	mu	0.1026807	0.2899736	-0.3589428
sigma	0.0031467	0.2238160	-0.3291366	sigma	0.2899736	1.2303463	-1.6290913
Q	0.0125013	-0.3291366	0.5057176	Q	-0.3589428	-1.6290913	2.1837103

Diagnostics – gengamma

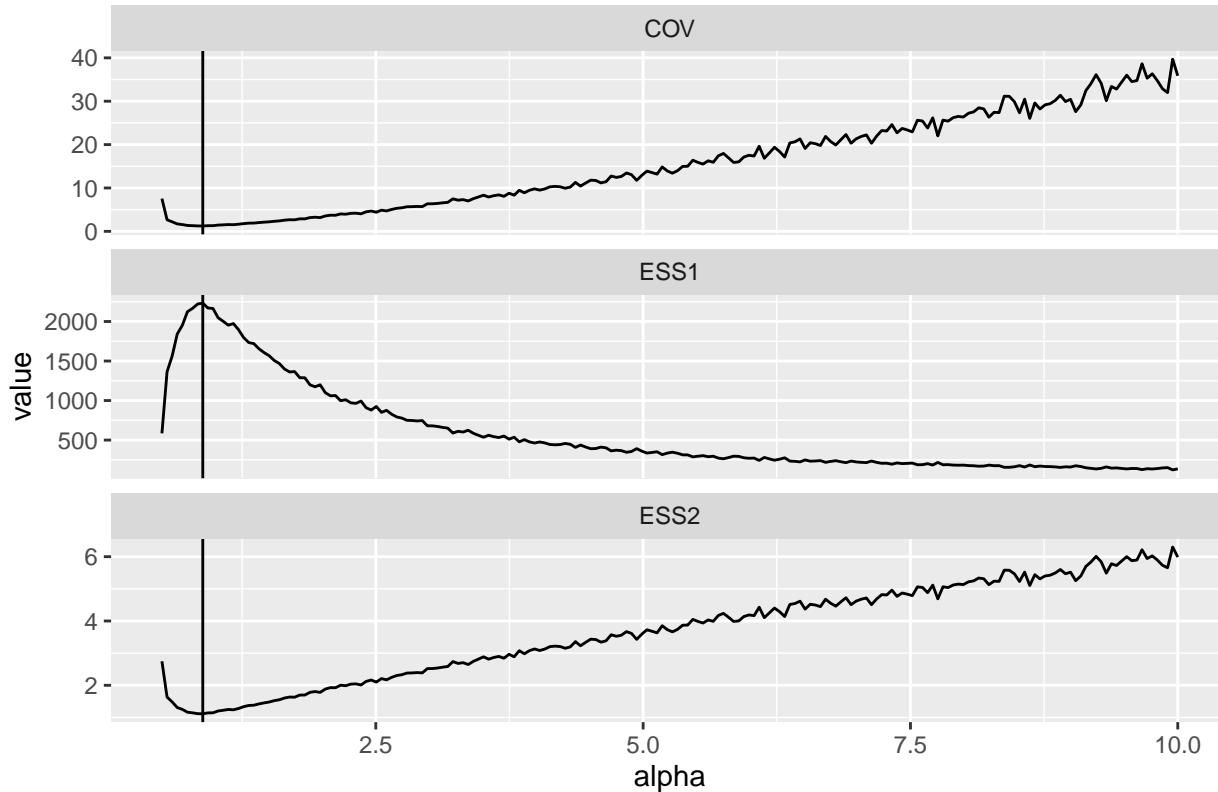


Figure 16: Importance sampling diagnostics: coefficient of variation (COV) and effective sample size (ESS) as functions of the tempering parameter alpha, Gen. Gamma distribution. The vertical line shows the optimal value of alpha identified by the algorithm.

Parameters – gengamma

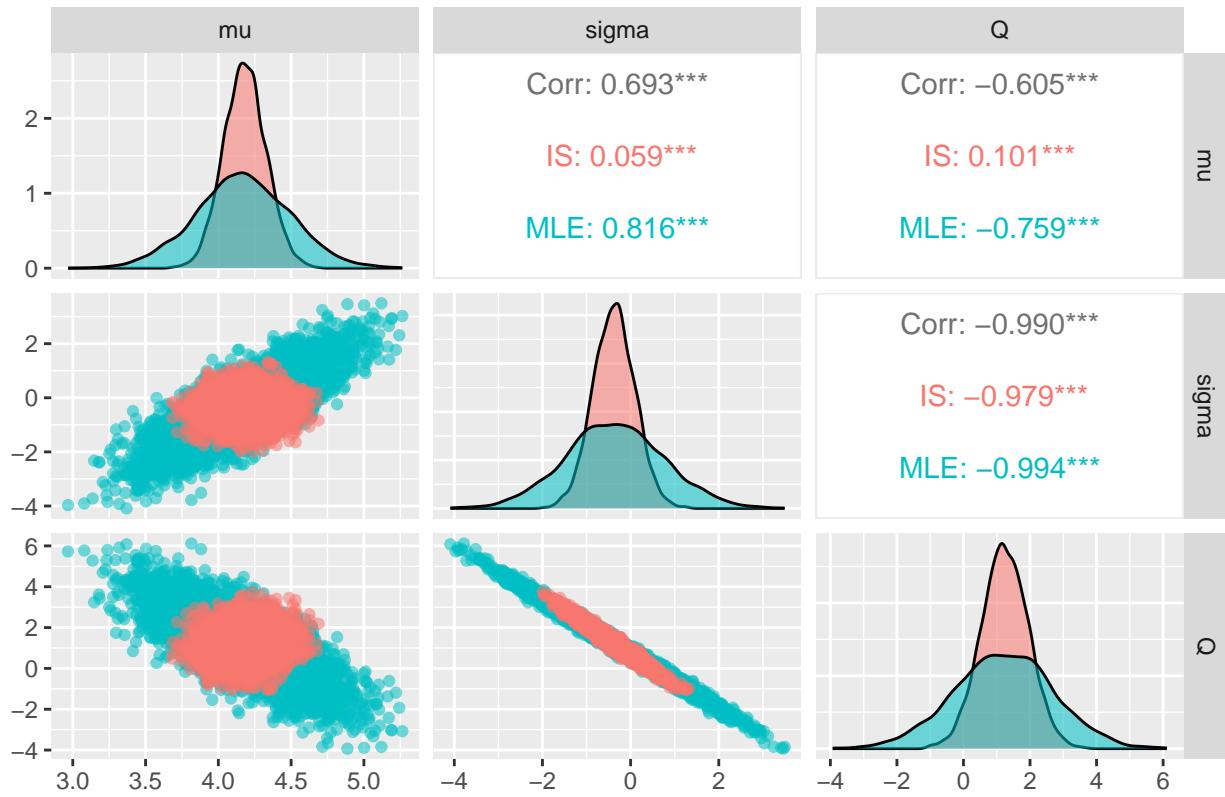


Figure 17: Survival curve parameter distributions and covariance estimates obtained using trial data only (MLE) and combining trial data with external information (IS), Gen. Gamma distribution

Survival – gengamma

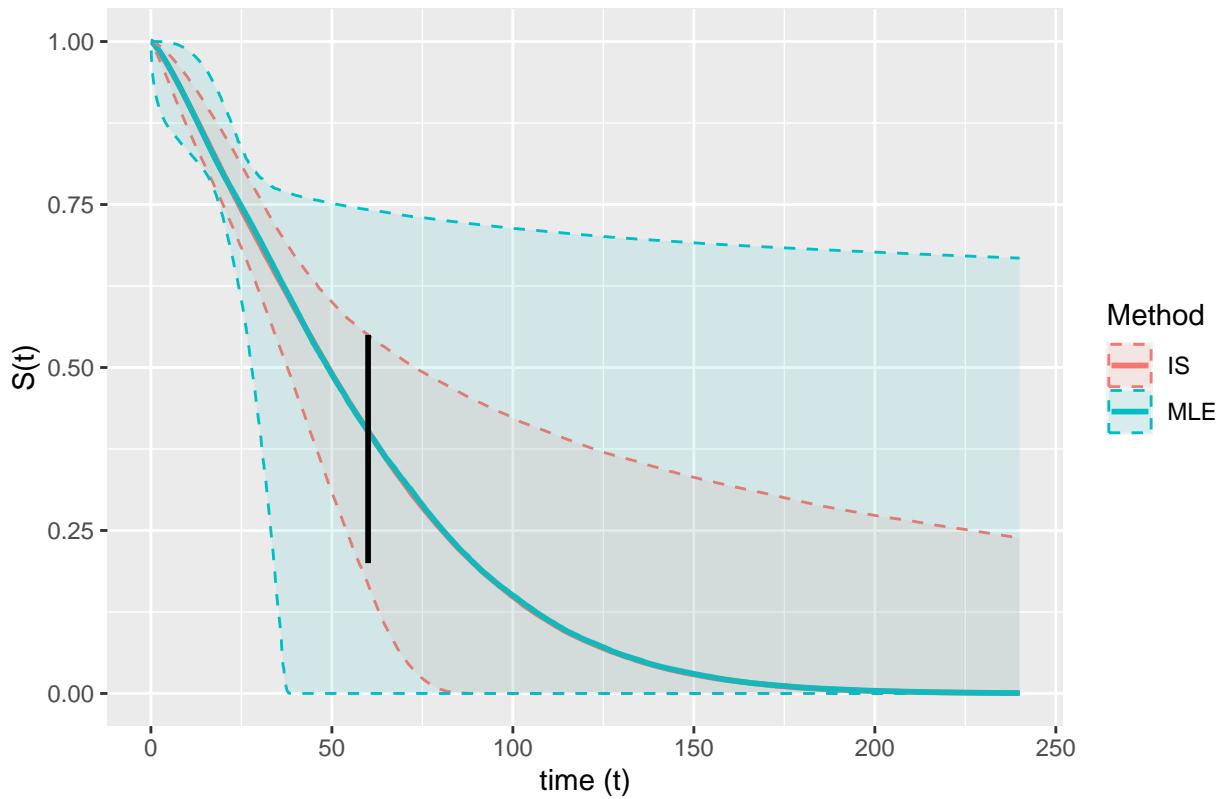


Figure 18: Survival curves (median and 95% confidence intervals) obtained using trial data only (MLE) and combining trial data with external information (IS), Gen. Gamma distribution

1.1 Parameter variability

Table 13 shows ‘Generalised variance,’ i.e., determinants of variance-covariance matrices, of the parameter estimates obtained using trial data only (MLE) and combining trial data with external information (IS). Formally, the generalised variance gives the area of the 95% highest density ellipse and can be interpreted as a 1-parameter measure of parameter uncertainty, see e.g., <https://stats.stackexchange.com/questions/12762/measure-of-spread-of-a-multivariate-normal-distribution>.

Table 13: Generalised variance of model parameter distributions. Comparison between parameter estimates obtained using trial data only (MLE) and combining trial data with external information (IS).

Distribution	Distance	MLE.Variance	IS.Variance	Ratio
exponential	0.0957855	0.0169491	0.0138444	0.8168193
weibull	0.0413796	0.0001670	0.0000827	0.4948566
gompertz	0.1474564	0.0000114	0.0000013	0.1140791
lognormal	0.3260830	0.0001878	0.0001435	0.7641277
llogis	0.1461963	0.0001754	0.0001134	0.6466355
gengamma	0.0546778	0.0003562	0.0000405	0.1138456

2 Comparison with expertsurv output

2.1 Plots of survival curves over time

Figures 19 to 24 show comparisons of survival curves (median and 95% confidence/credible intervals) obtained from the importance sampling method described in the paper, with those obtained from the fully Bayesian approach of Cooney & White implemented in the expertsurv package.

Survival curves for the exponential, Weibull, Gompertz and log-logistic models were almost identical between the two methods. For the log-normal and generalised gamma models (Figures 22 and 24), there was a small but notable shift in the parameter distribution and corresponding survival estimates. The reason for this is not immediately clear. However, in both cases the impact was small and mostly evident in the tails of the survival distributions.

Survival - Exponential

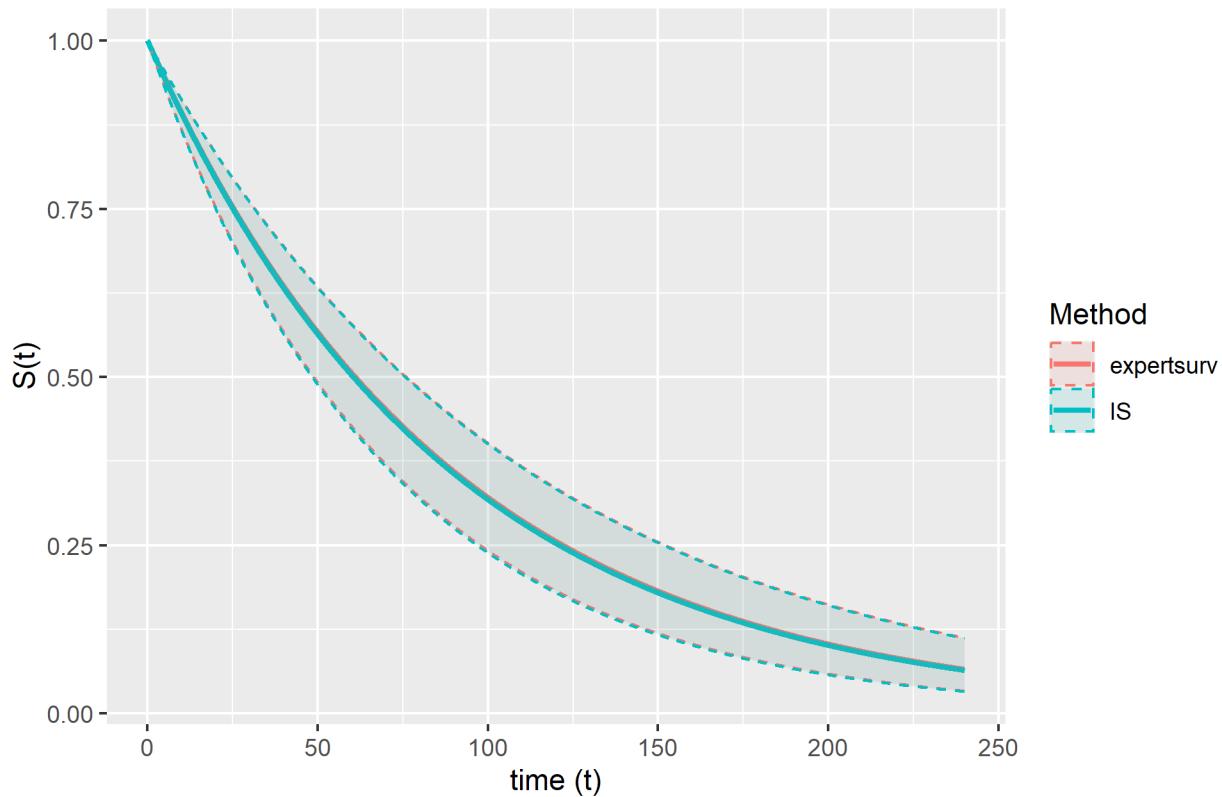


Figure 19: Survival curves (median and 95% confidence intervals) obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Exponential distribution

Survival - Weibull

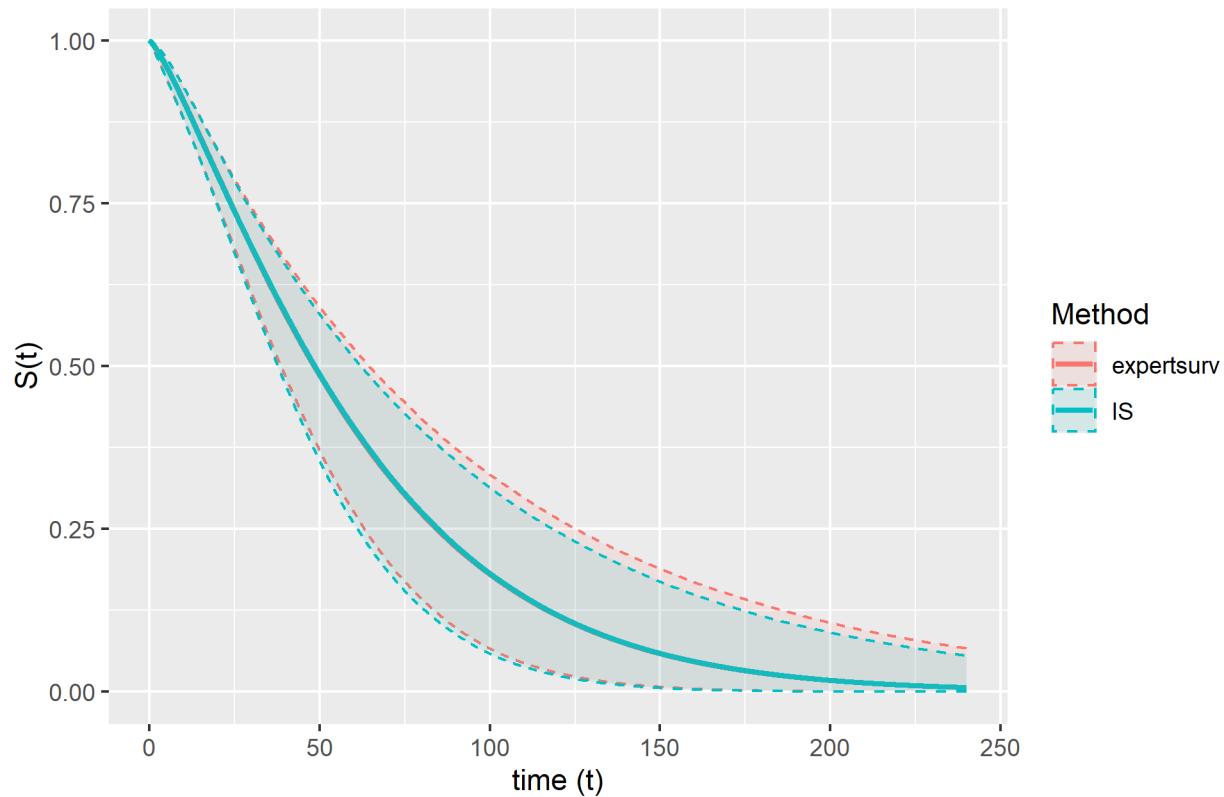


Figure 20: Survival curves (median and 95% confidence intervals) obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Weibull distribution

Survival - Gompertz

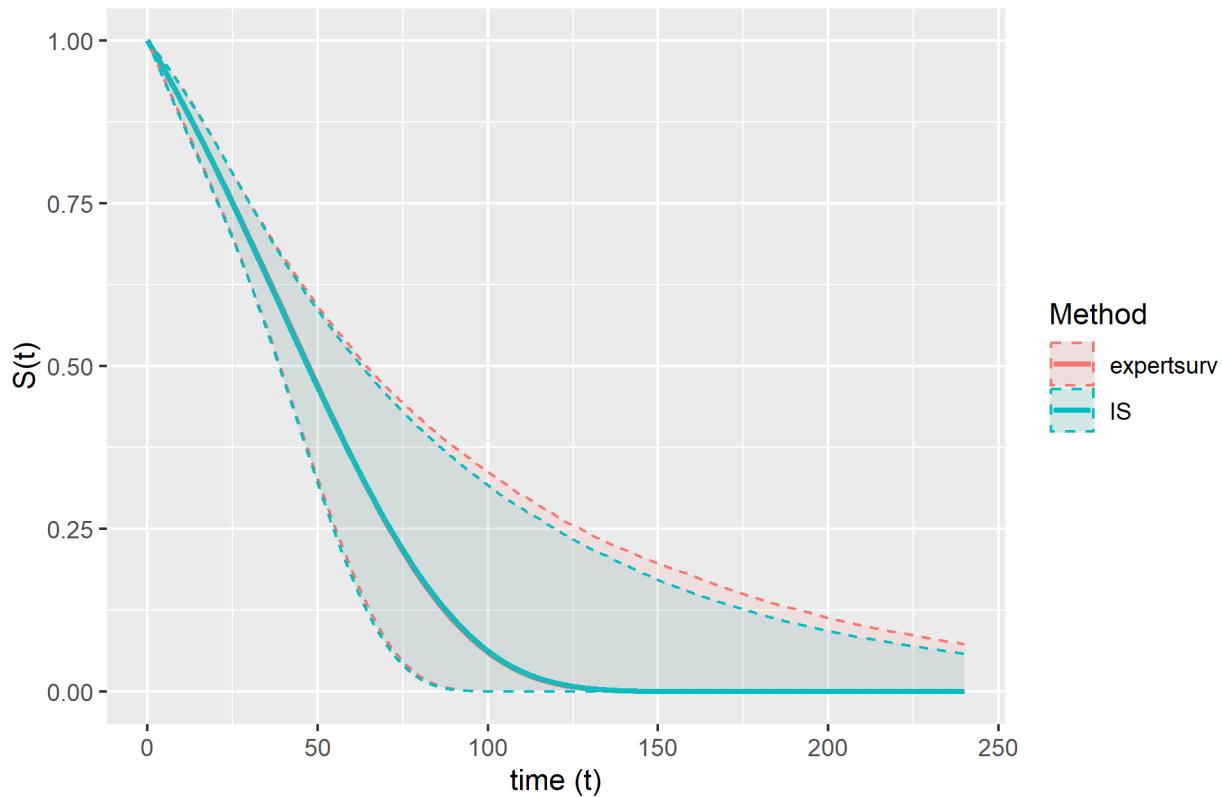


Figure 21: Survival curves (median and 95% confidence intervals) obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Log-normal distribution

Survival - Log-normal

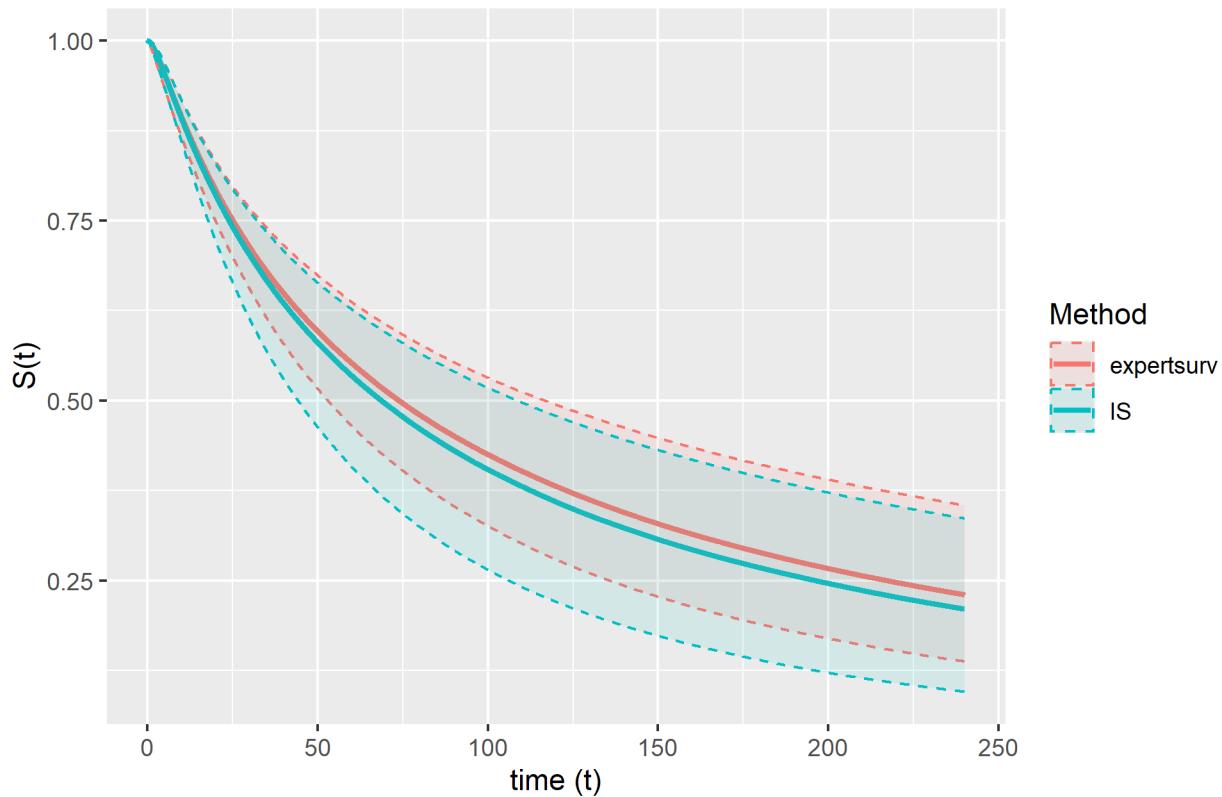


Figure 22: Survival curves (median and 95% confidence intervals) obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Log-logistic distribution

Survival - Log-logistic

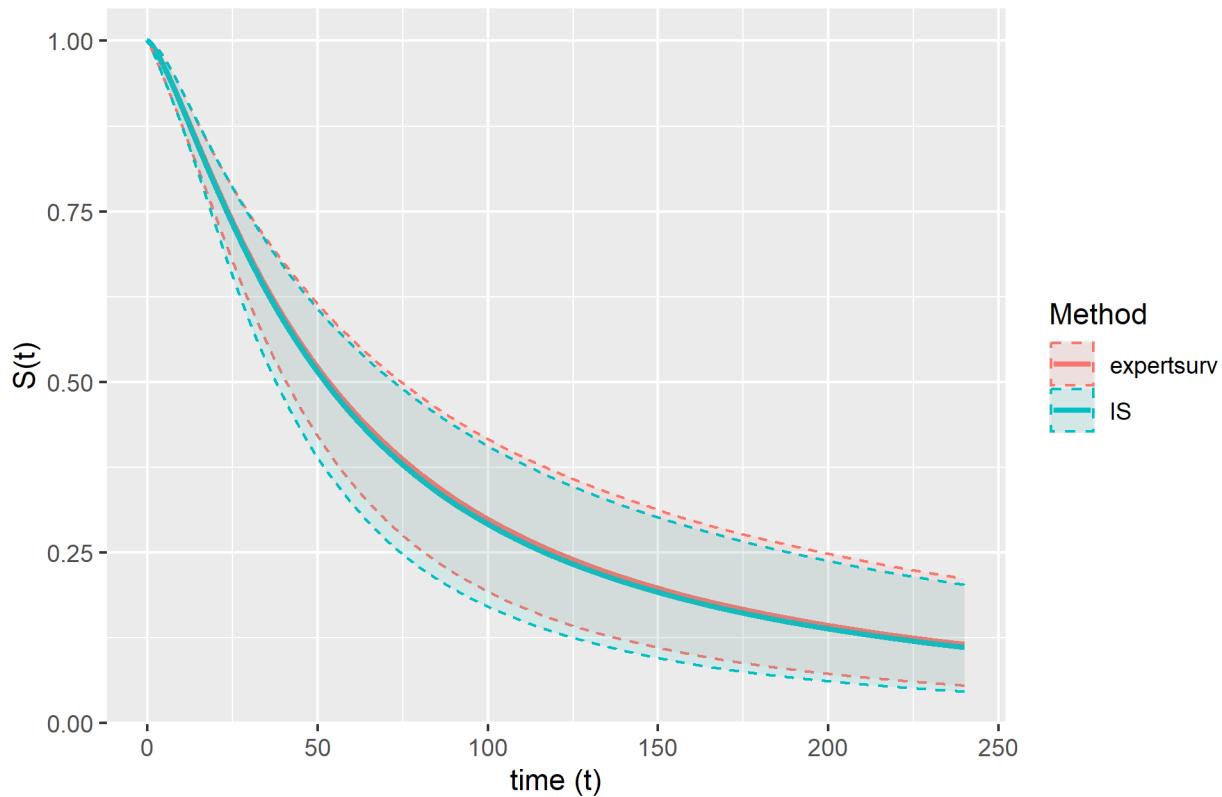


Figure 23: Survival curves (median and 95% confidence intervals) obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Gompertz distribution

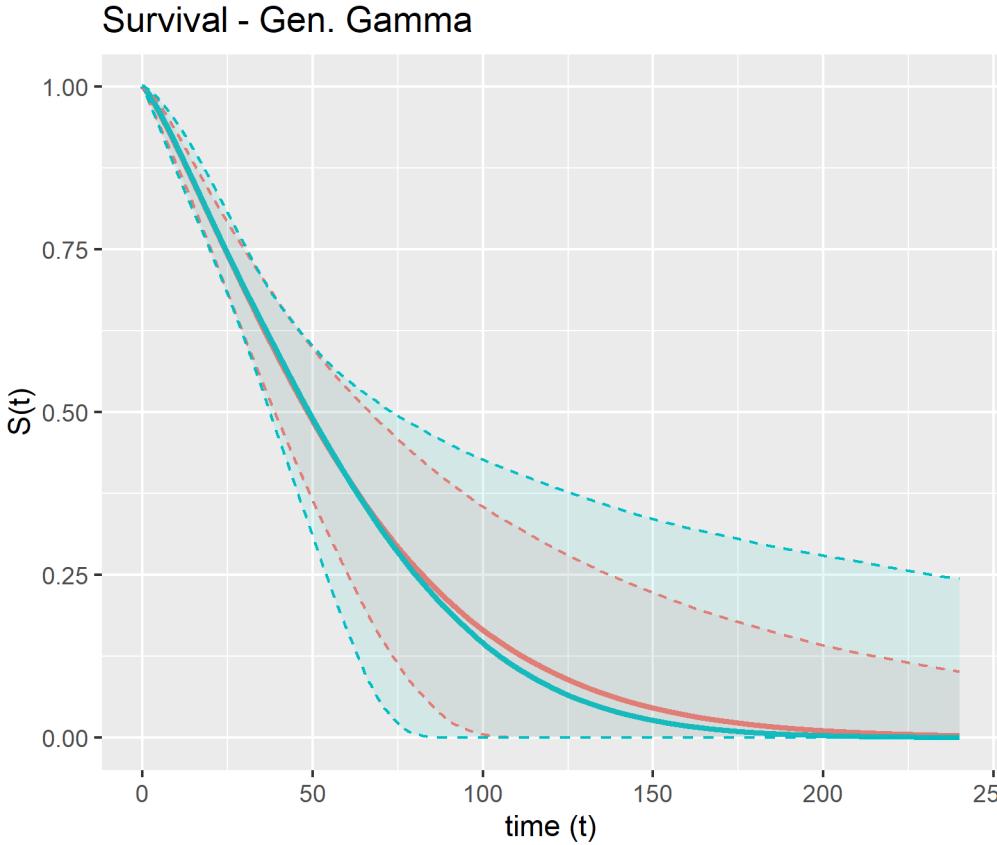


Figure 24: Survival curves (median and 95% confidence intervals) obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Gen. Gamma distribution

2.1.1 Comparisons of parameter distributions

Figures 25 to 30 compare survival curve parameter distributions obtained from the importance sampling method described in the paper, with those obtained from the fully Bayesian approach of Cooney & Whilte implemented in the expertsurv package. Again, some differences are evidence between the two methods for the log-normal and generalised gamma models (Figures 28 and 30).

Parameters – Exponential

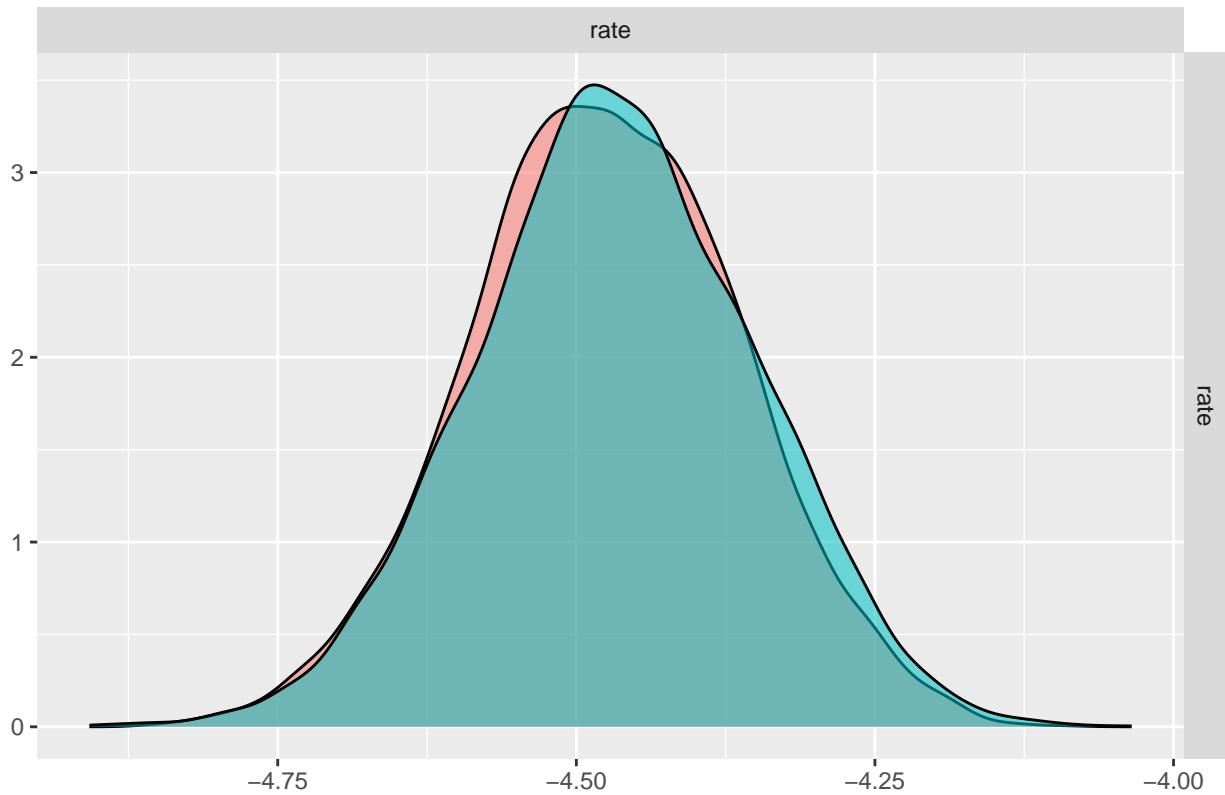


Figure 25: Survival curve parameter distributions and covariance estimates obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Exponential distribution

Parameters – Weibull

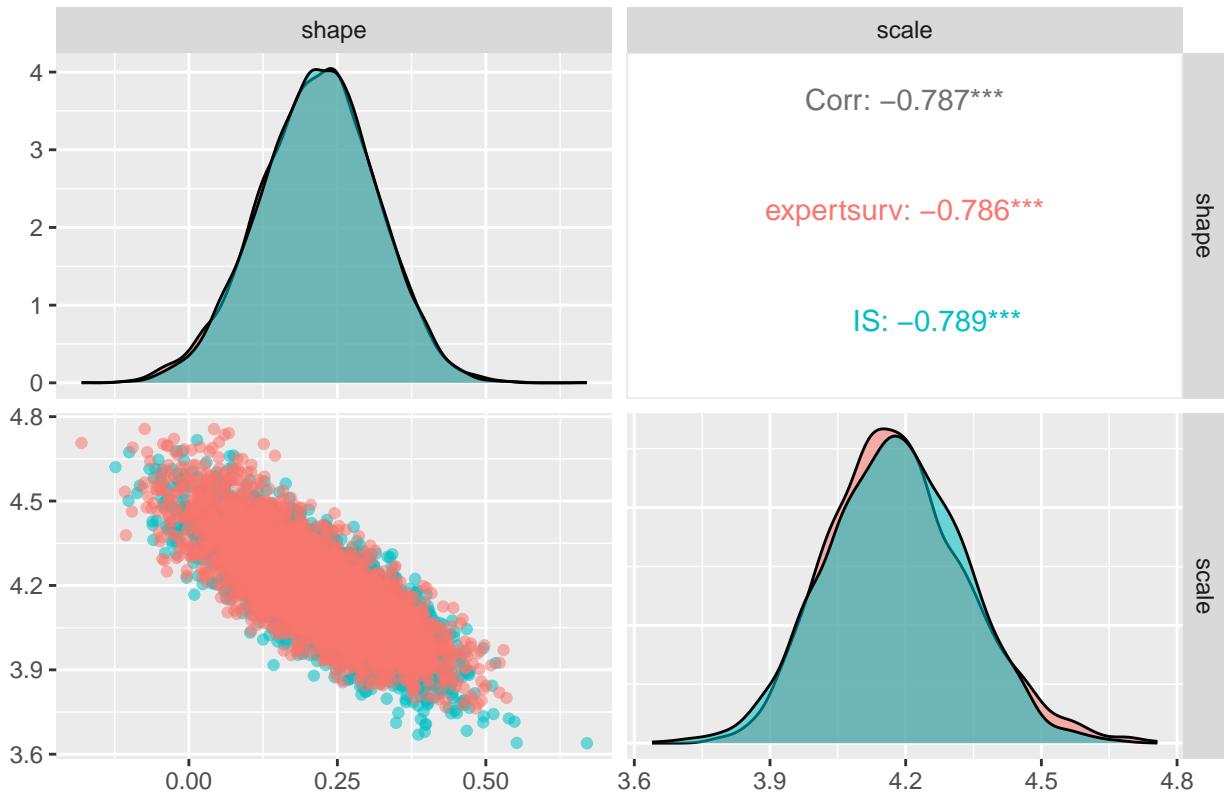


Figure 26: Survival curve parameter distributions and covariance estimates obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Weibull distribution

Parameters – Gompertz

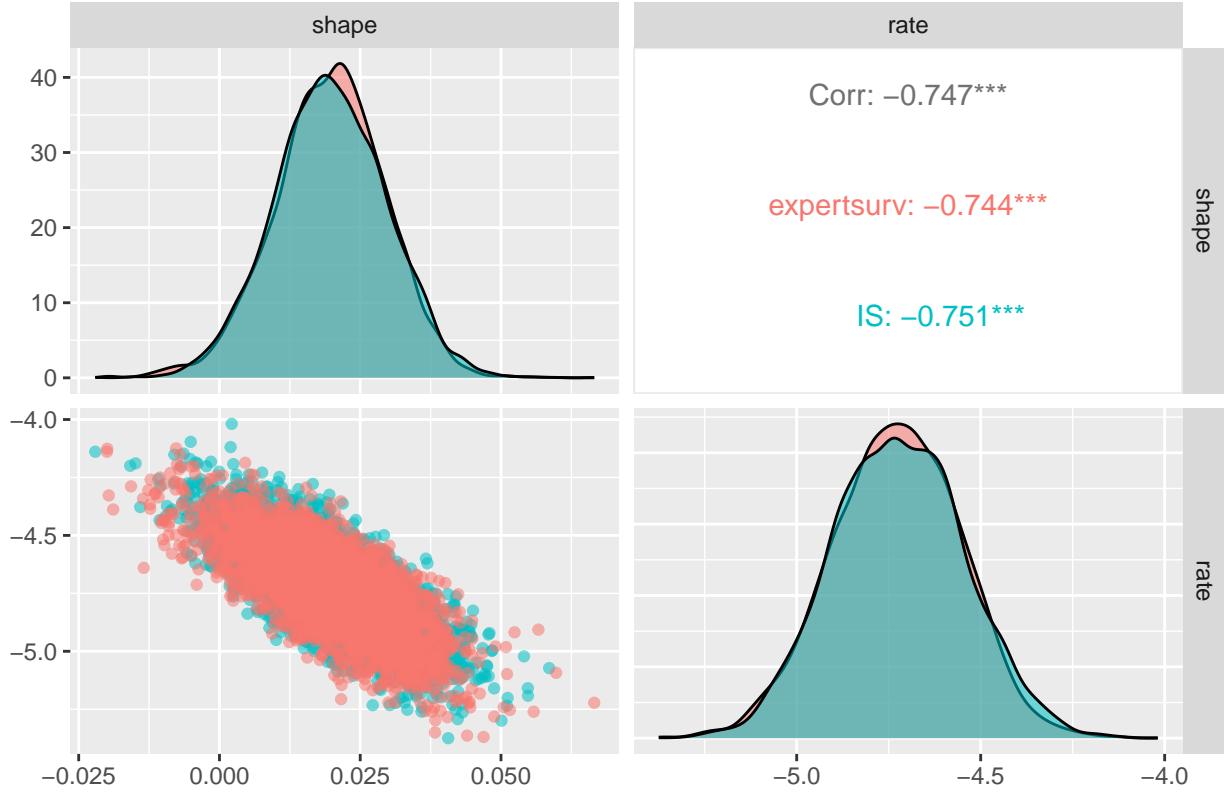


Figure 27: Survival curve parameter distributions and covariance estimates obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Log-normal distribution

Parameters – Log–normal

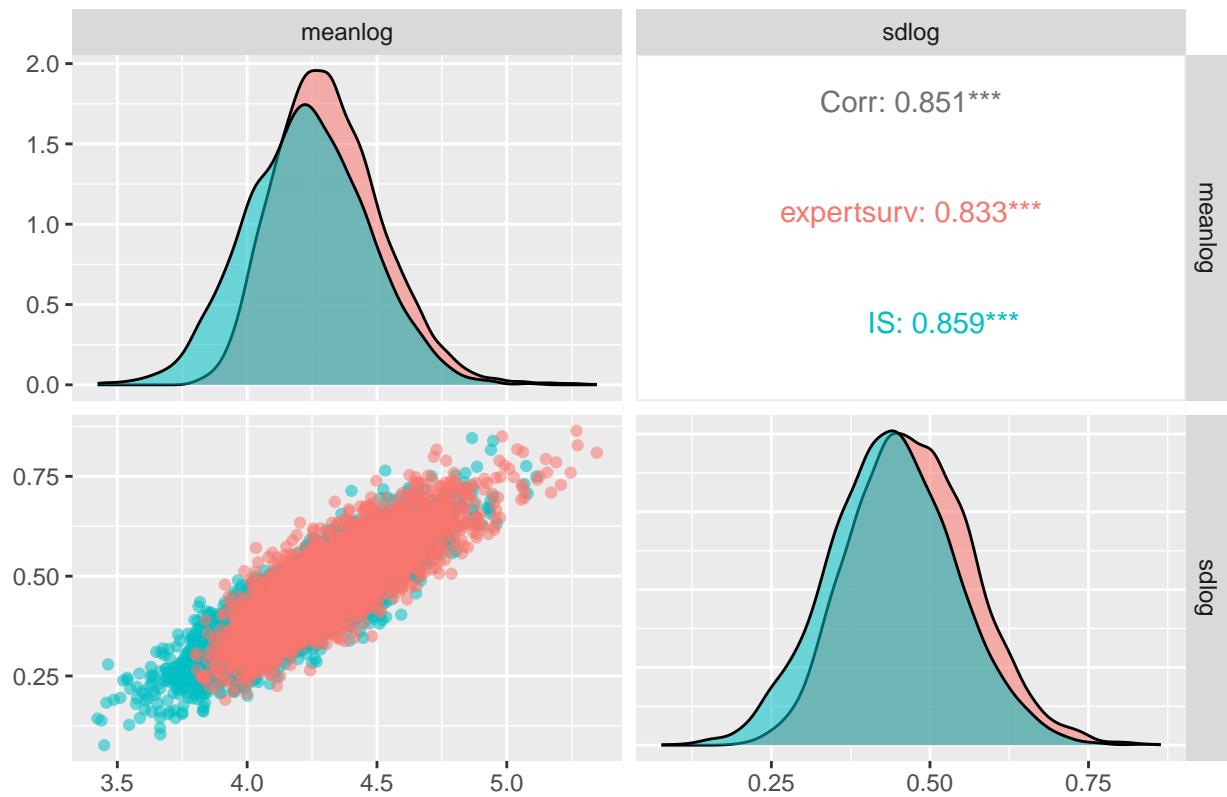


Figure 28: Survival curve parameter distributions and covariance estimates obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Log-logistic distribution

Parameters – Log-logistic

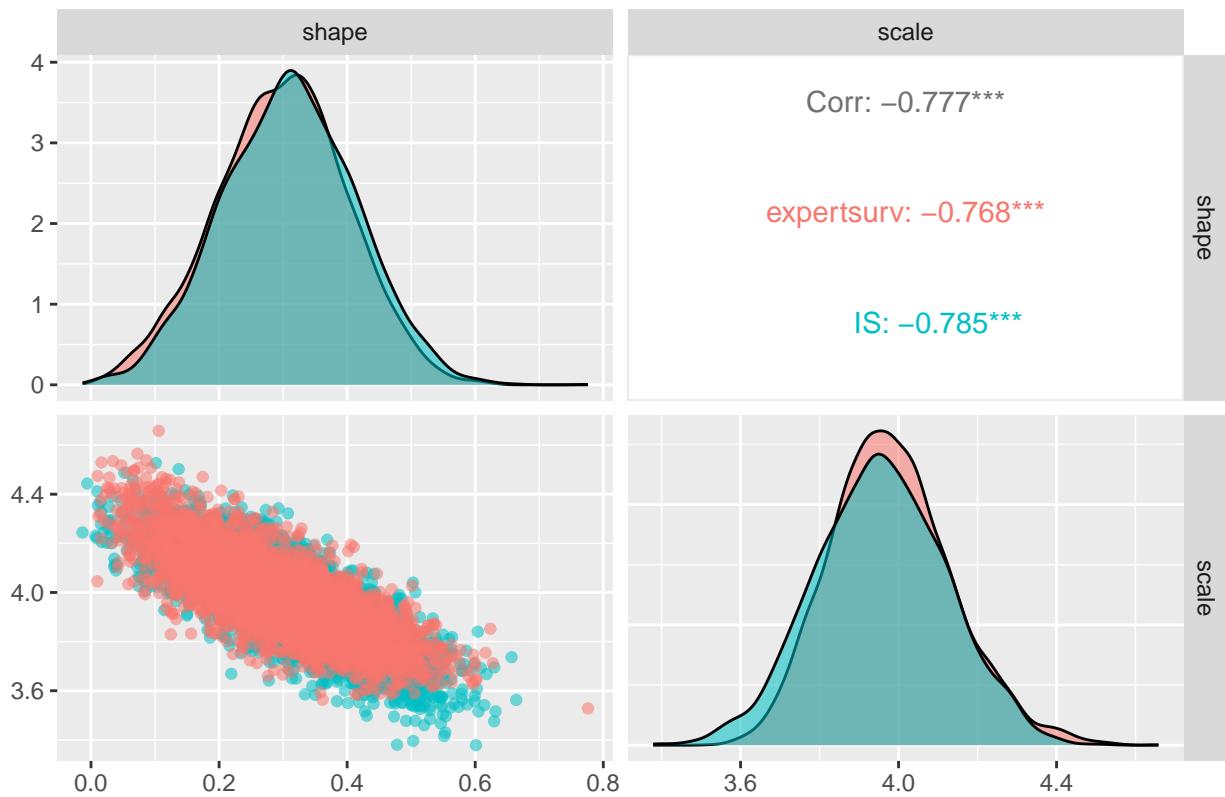


Figure 29: Survival curve parameter distributions and covariance estimates obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Gompertz distribution

Table 14: Comparison of probabilistic total area under the curve (mean lifetime OS) estimates, obtained from combining trial data with external information using the importance sampling (IS) method described in the paper, and with the fully Bayesian method of Cooney and White implemented in the expertsurv package. Values shown are probabilistic mean and 95 percent confidence/credible intervals.

Distribution	expertsurv	IS	Mean.Diff	Var.Ratio
Exponential	88.48 (70.48, 109.73)	87.74 (69.78, 109.28)	-0.74	1.06
Gen. Gamma	62.23 (42.85, 103.18)	71.11 (38.84, 216.27)	8.88	8.73
Gompertz	55.85 (39.56, 92.84)	53.89 (39.24, 85.24)	-1.96	0.44
Log-logistic	123.17 (77.65, 189.59)	119.06 (71.11, 181.96)	-4.11	1.01
Log-normal	202.54 (126.08, 311.84)	183.80 (97.93, 295.22)	-18.74	1.07
Weibull	62.43 (45.73, 90.16)	61.93 (44.18, 85.17)	-0.50	0.90

Parameters – Gen. Gamma

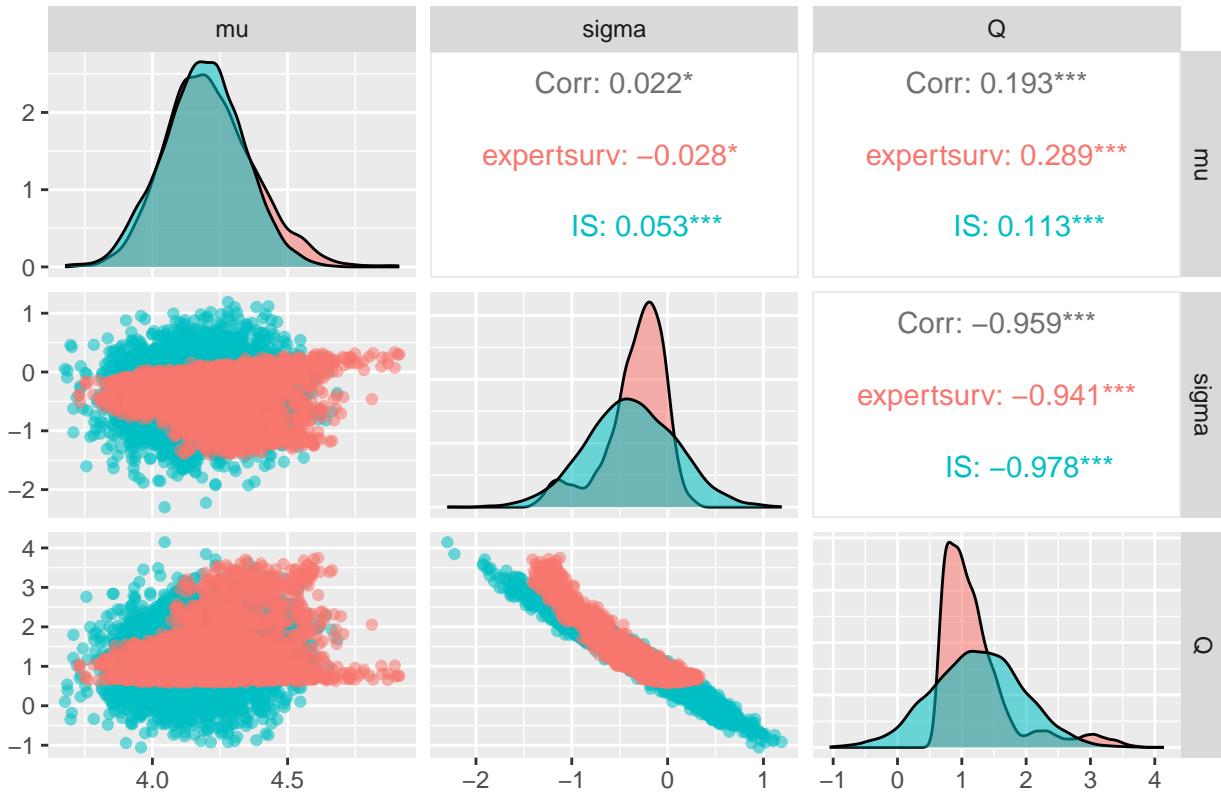


Figure 30: Survival curve parameter distributions and covariance estimates obtained by combining trial data with external information using the importance sampling (IS) and expertsurv methods, Gen. Gamma distribution

2.2 Comparisons of AUC distributions

Table 14 and Figure 31 compare probabilistic estimates of area under the curve between the two methods. In general, AUC measures (population) mean survival extrapolated over a lifetime, though in these examples survival is capped at 100 years since some curves plateau.

Table 15: Comparison of 5-year OS estimates, obtained from combining trial data with external information using the importance sampling (IS) method described in the paper, with the fully Bayesian method of Cooney and White implemented in the `expertsurv` package.

Distribution	Output	mean	median	sd	lwr.95	upr.95
Exponential	IS	50.16%	50.28%	4.03%	42.32%	57.75%
Exponential	<code>expertsurv</code>	50.47%	50.56%	3.87%	42.68%	57.88%
Gen. Gamma	IS	38.94%	40.11%	9.74%	16.65%	55.04%
Gen. Gamma	<code>expertsurv</code>	40.08%	40.03%	7.12%	25.45%	53.88%
Gompertz	IS	35.63%	35.98%	8.87%	17.68%	51.87%
Gompertz	<code>expertsurv</code>	35.89%	36.01%	8.71%	18.84%	52.77%
Log-logistic	IS	44.89%	45.25%	5.98%	32.21%	55.46%
Log-logistic	<code>expertsurv</code>	45.88%	45.95%	5.37%	35.19%	56.30%
Log-normal	IS	52.94%	53.44%	5.72%	40.77%	62.69%
Log-normal	<code>expertsurv</code>	55.11%	55.20%	4.50%	46.42%	63.67%
Weibull	IS	40.05%	40.56%	6.65%	25.86%	51.30%
Weibull	<code>expertsurv</code>	40.32%	40.41%	6.53%	27.64%	52.69%

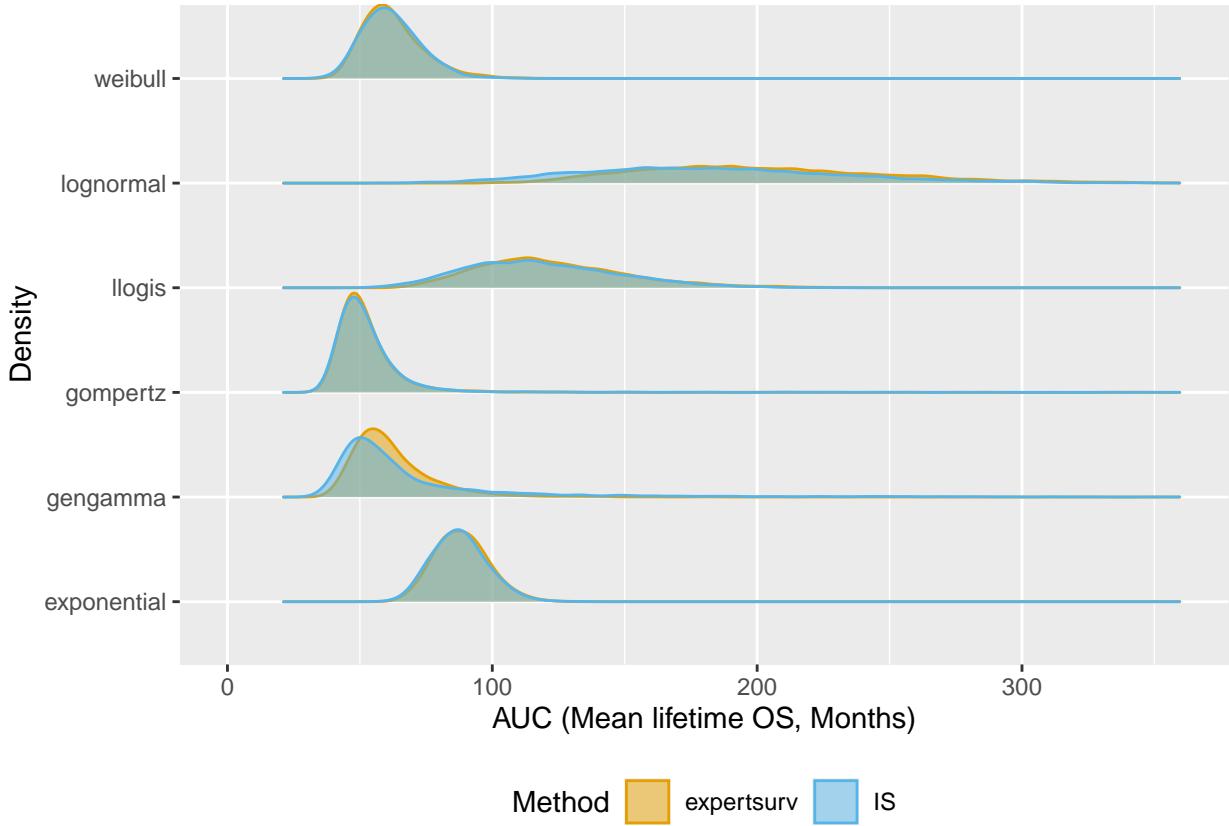


Figure 31: Density plots comparing probabilistic total area under the curve (mean OS) distributions obtained from combining trial data with external information using the importance sampling (IS) method described in the paper, with those obtained from the fully Bayesian method of Cooney and White implemented in the `expertsurv` package.

2.3 Comparisons of 5-year OS

Table 15 and Figure 32 compare probabilistic estimates of 5-year OS obtained from the two methods.

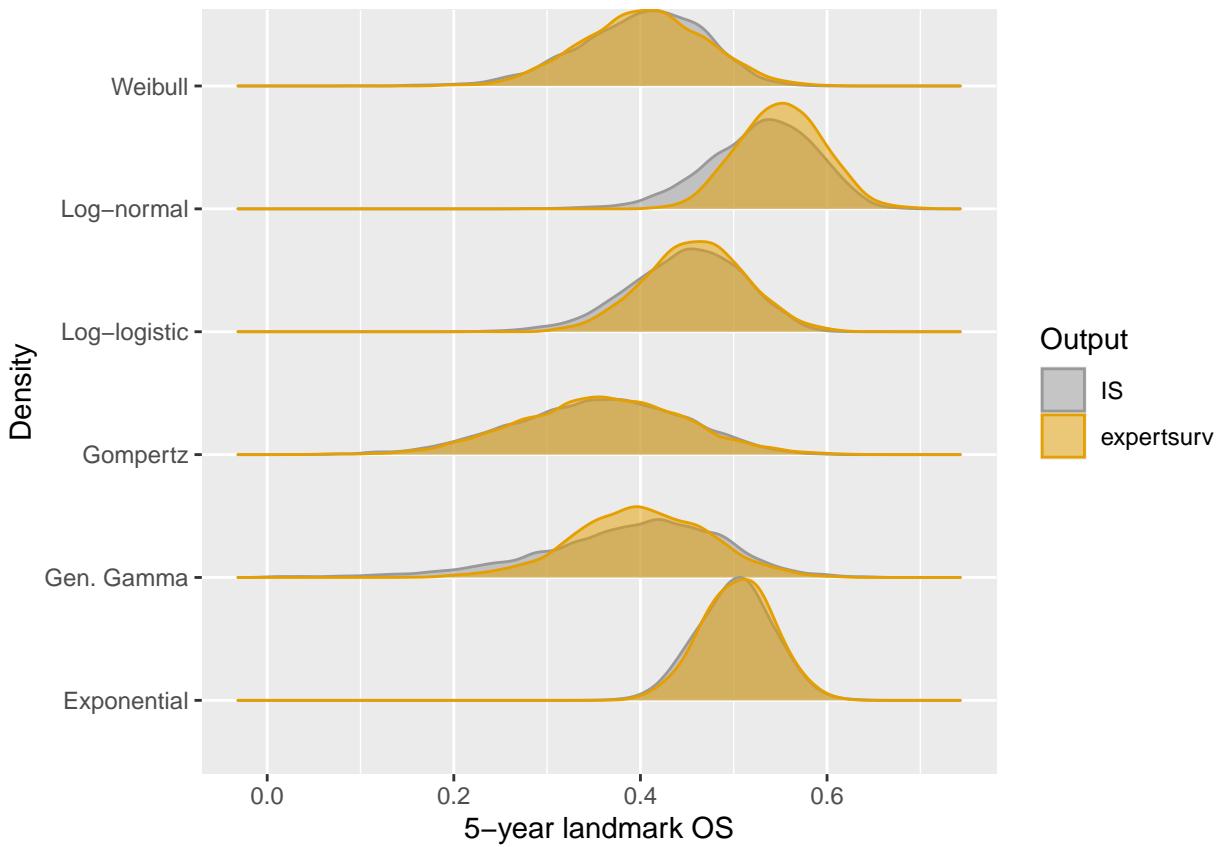


Figure 32: Density plots comparing 5-year OS estimates, obtained from combining trial data with external information using the importance sampling (IS) method described in the paper, with those obtained from the fully Bayesian method of Cooney and White implemented in the expertsurv package.