A Simulation Study Comparing the Performance of the Linear Regression, Daniel and Hughes, and Bivariate Random Effect Meta-Analysis (BRMA) Models of Surrogacy Relationships for Treatment Effects

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OBJECTIVES: Analysis of treatment effects on surrogate endpoints may be useful where final endpoints are not recorded in trials (e.g. long-term cardiovascular endpoints) or where estimated treatment effects on final endpoints are uncertain (e.g. overall survival in populations with good prognosis). The estimated relationship between final and surrogate endpoints may be used for the purposes of inference or estimation regarding treatment effects on final endpoints. In this simulation study we compare the performance of linear regression (LM), Daniel and Hughes (DH) and Bivariate Random effect Meta-Analysis (BRMA) in estimating the relationship between a surrogate and final (decision-relevant) endpoints (Bujkiewicz et al. (2019) .

METHODS: In the example analysis presented here, 5000 sets of treatment effect data for final and surrogate endpoints with 30 studies in each set were simulated using a multivariate normal distribution. Simulations were run both with the standard deviation (SD) set to be equal for the final and surrogate endpoints (0.4) and greater for the final endpoints (final = 0.8, surrogate =0.4). Within study correlation was set to 0.5, between study SD was set 1 for the final and surrogate endpoints.

The regression coefficient predicting the treatment effects for the final endpoint as a function of the surrogate endpoint were estimated using the LM, DH and BRMA models. The bias (mean difference between the estimate and true value for the co-efficient) and coverage (proportion of 95% CrIs including the true value) were estimated for each estimator.

RESULTS: The results for the analysis where the standard deviation was set to be equal for the final and surrogate endpoints is shown in Box 1 and results where it was greater for the final endpoint are shown in Box 2. The graphs below the results tables shown data from an example set of simulated data form each of the analytic approaches. The graphs in each set show the estimated study data; the estimated relationship between the final and surrogate endpoints with a marginal density plot showing the distribution of the observed data and the predicted values from the model; and the relationship between modelled and predicted value for each study.

Where the variance is equal for final and surrogate endpoints, the BRMA model performs the best in terms of bias although the coverage statistics suggests that the width of confidence interval is over-estimated. The bias is greatest for the LM model and both the LM and DH models appear to under-estimate the width of the confidence interval.

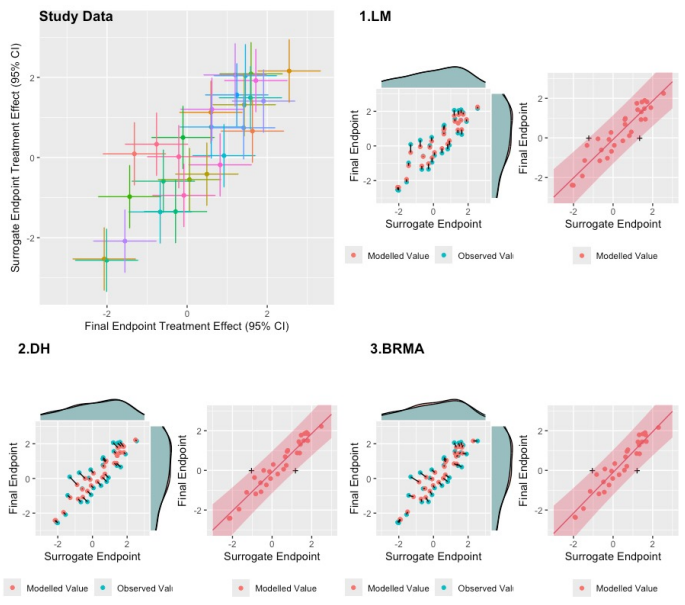
Where the variance is greater for final endpoint, the bias is greatest with the BRMA model, and the coverage statistics suggests that the width of confidence interval is over-estimated. The Bias is lowest for the DH model.

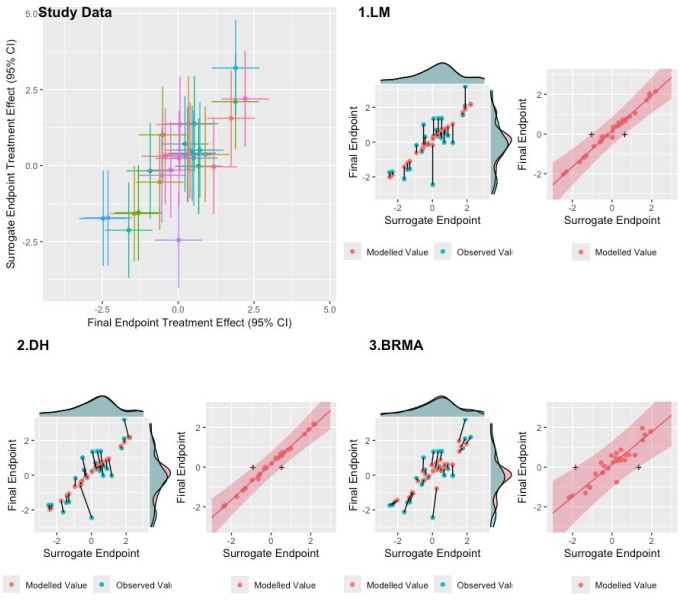
Box 1. Variance equal for final and surrogate endpoints

Model	Estimated regression co-efficient for final endpoint as a function of surrogate endpoint			
	Mean	SD	Bias	Coverage
LM	0.759	0.126	-0.0409	0.934
DH	0.762	0.126	-0.0381	0.936
BRMA	0.823	0.142	0.0235	0.980

Box 2. Variance greater for final and endpoint

Model	Estimated regression co-efficient for final endpoint as a function of surrogate endpoint			
	Mean	SD	Bias	Coverage
LM	0.829	0.165	0.0286	0.950
DH	0.817	0.162	0.0168	0.960
BRMA	0.764	0.196	-0.0364	0.974





Discussion: Where the within study variance was equal for treatment effects for the final and surrogate endpoints, the BRMA model was the best performing model. However, where the variance was greater for treatment effects on the final endpoint, the DH model was the best performing model, with lower bias. This may reflect the greater shrinkage to the mean of study estimates for the final endpoint compared to the surrogate in the BRMA model. This observation is important as it is likely that the variance of the final endpoint will be greater than the surrogate endpoint in most surrogacy analyses.

References: Bujkiewicz et al. (2019) Statistics in Medicine. 2019;38:3322–3341. Bujkiewicz et al. (2019) NICE DSU TSD 20