# Bayesian Joint Benefit-Risk Copula Model Calibration

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## Introduction

- Bayesian copula models provide a flexible, interpretable framework to jointly model multivariate benefit and risk outcomes; models for marginal outcomes and dependency between outcomes are specified separately
- Simulation studies are used to explore the calibration of posterior parameter estimates as a function of continuous/discrete outcome type, correlation between outcomes, prior specification, and sample size

## Model

The normal copula model is

$$C_\rho^{Norm}(u_1, u_2) = \Phi_2(\Phi^{-1}(u_1), \Phi^{-1}(u_2)|\rho)$$

For efficacy outcome $Y_E$ and safety outcome $Y_S$ with distribution functions $F_E$ and $F_S$ the joint bivariate distribution function is

$$H(y_e, y_s) = C_\rho^{Norm}(F_E(y_e; \eta_e), F_S(y_s; \eta_s)|\rho)$$

- Identity or probit link GLMs with a binary treatment indicator used for marginal models of $Y_E$ and $Y_S$
- The dependency parameter $\rho$ was allowed to vary by treatment group
- Values for each parameter were drawn from either a location-scale $Beta$ distribution (proportions and correlations) or a $Normal$ distribution (means) based on the scenario and used to generate data
- A normal copula model with flat, weakly informative, or boundary-avoiding priors was fit for each scenario using RStan to get 5000 posterior samples
- Mean posterior parameter values were compared to the true drawn parameters

## Simulation Scenarios

1) Binary $Y_E$ and $Y_S$

- Placebo group:
  - $\Pr(Y_E = 1) = p_{e,pbo} = 0.2$
  - $\Pr(Y_S = 1) = p_{s,pbo} = 0.1$
  - (tetrachoric) correlation $\rho_{pbo} = 0.1$
- Treatment group:
  - $\Pr(Y_E = 1) = p_{e,trt} = 0.2\,, 0.5$ or $0.8$
  - $\Pr(Y_S = 1) = p_{s,trt} = 0.1\,, 0.4$ or $0.7$
  - (tetrachoric) correlation $\rho_{trt} = 0.1, 0.35$ or $0.6$

2) Continuous $Y_E$, binary $Y_S$

- Placebo group:
  - $E[Y_E] = \mu_{pbo} = -150$
  - $\Pr(Y_S = 1) = p_{s,pbo} = 0.1$
  - (polyserial) correlation $\rho_{pbo} = 0.1$
- Treatment group:
  - $E[Y_E] = \mu_{trt} = -150\,, -50$ or $0$
  - $\Pr(Y_S = 1) = p_{s,trt} = 0.1\,, 0.4$ or $0.7$
  - (polyserial) correlation $\rho_{trt} = 0.1, 0.35$ or $0.6$

3) Continuous $Y_E$ and $Y_S$

- Placebo group:
  - $E[Y_E] = \mu_{e,pbo} = -150$
  - $E[Y_S] = \mu_{s,pbo} = -150$
  - Pearson correlation $\rho_{pbo} = 0.1$
- Treatment group:
  - $E[Y_E] = \mu_{e,trt} = -150\,, -50$ or $0$
  - $E[Y_S] = \mu_{s,trt} = -150\,, -50$ or $0$
  - Pearson correlation $\rho_{trt} = 0.1, 0.35$ or $0.6$

For all scenarios $n$ per arm$= 50,\ 100$ or $200$. Fifty replicates were used for each parameter/sample size/model prior combination

## Results

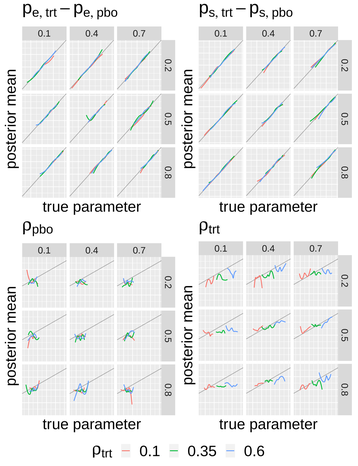


**Figure 1:** Scenario 1 with flat priors and $n = 50$ per arm

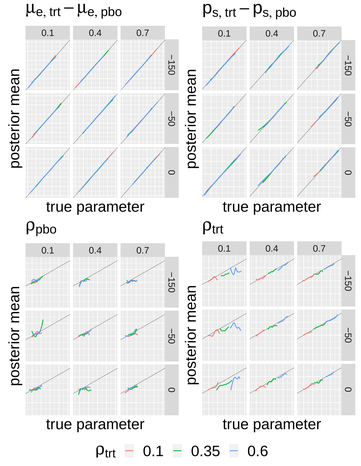


**Figure 2:** Scenario 2 with weakly informative priors and $n = 200$ per arm

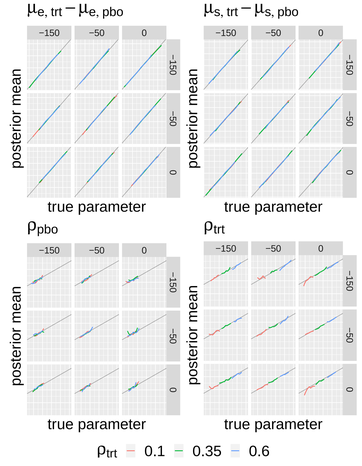


**Figure 3:** Scenario 3 with boundary-avoiding priors and $n = 100$ per arm

## Conclusions

- Average posterior mean differences (e.g. $\mu_{e,trt} - \mu_{e,pbo}$) and risk differences (e.g. $p_{s,trt} - p_{s,pbo}$) for all marginal model parameters were reasonably well-calibrated under all simulation scenarios and 243 combinations of parameters, sample size, and model priors despite miscalibration of the posterior dependency parameters
- The mixed continuous/discrete simulation setting was the most difficult model to estimate using MCMC as measured by the average number of divergences per simulation (scenario 1: 33 divergences, scenario 2: 834 divergences, scenario 3: 0 divergences)
- All posterior parameters (marginal and copula dependence) were well-calibrated for scenario 3 which is equivalent to a multivariate probit regression allowing the covariance between outcomes to differ by treatment
- Differences in prior specification were most evident for dependency parameters in scenario 1 (binary $Y_E$ and $Y_S$)
- Increasing sample size had the greatest effect on calibration of the treatment group dependency parameter for the discrete/discrete simulation setting

## References

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2. Costa, Maria, and Thomas Drury "Bayesian joint modelling of benefit and risk in drug development." *Pharm. Stat.* (2018)
3. Stan Development Team. 2018. RStan: the R interface to Stan. R package version 2.19.2. http://mc-stan.org
4. Joe, H. *Dependence Modeling with Copulas* CRC Press, Boca Raton. (2015)

All R code and Stan functions for simulations are available at: https://github.com/ntjames/asa_biopharm_2019