Operating Characteristics of Bayesian Joint Benefit-Risk Copula Models

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Introduction:

- To receive regulatory approval, the benefits of an intervention must outweigh its risks
- Clinical trials often evaluate efficacy and safety outcomes with separate models
- Bayesian copula models provide a flexible, interpretable approach to jointly model multivariate benefit and risk outcomes
- Models for each marginal outcome and dependency between outcomes are specified separately
- We explore operating characteristics under the joint copula modeling approach and using with separate independent models

Model:

- For efficacy outcome Y_1 and safety outcome Y_2 with distribution functions F_1 and F_2 the normal copula model is

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

and the joint bivariate outcome distribution function is

$$H(y_1, y_2) = C_\rho^{Norm}(F_1(y_1;\ \eta_1), F_2(y_2; \eta_2)|\rho)$$

- GLMs with identity or probit link are used for marginal models of Y_1 and Y_2 for both copula and separate models
- A single binary covariate indicated treatment group (placebo or treatment)
- The dependency parameter ρ is also allowed to vary by treatment group

Simulation Scenarios:

1) Binary efficacy, binary safety outcomes

Placebo group:
probability of efficacy $p_{E,\,pbo} = 0.2$
probability of adverse event $p_{S,\,pbo} = 0.1$
(tetrachoric) correlation $\rho_e = 0.1$

Treatment group:
probability of efficacy $p_{E,\,trt} = 0.2$, 0.5, or 0.8
probability of adverse event $p_{S,\,trt} = 0.2$, 0.5, or 0.8
(tetrachoric) correlation $\rho_t = 0.1$, 0.35, or 0.6

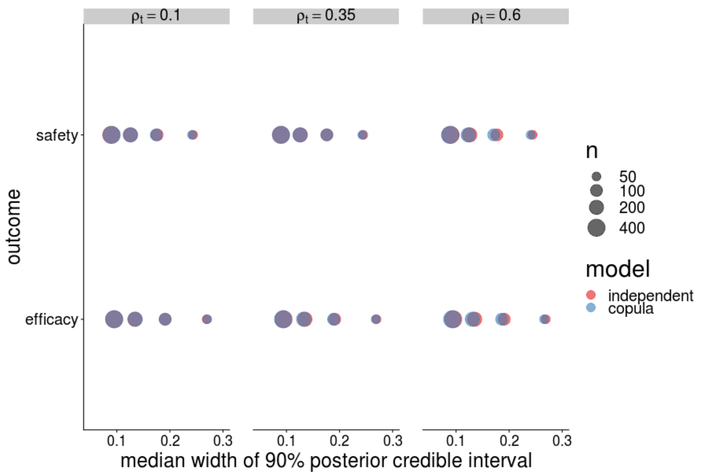
2) Continuous efficacy, binary safety outcomes

Placebo group:
efficacy change from baseline mean $\mu_{pbo} = -150$
efficacy change from baseline variance $\sigma^2_{pbo} = 100^2$
probability of adverse event $p_{S,\,pbo} = 0.1$
(polyserial) correlation $\rho_e = 0.1$

Treatment group:
efficacy change from baseline mean $\mu_{trt} = -150$, -50, 0
efficacy change from baseline variance $\sigma^2_{trt} = 100^2$
probability of adverse event $p_{S,\,trt} = 0.1$, 0.4, 0.7
(polyserial) correlation $\rho_t = 0.1$, 0.3, or 0.5

For both scenarios n per arm = 50, 100, 200, 400 with 100 repetitions for each combination of parameters

Credible Interval widths for binary-binary outcome:



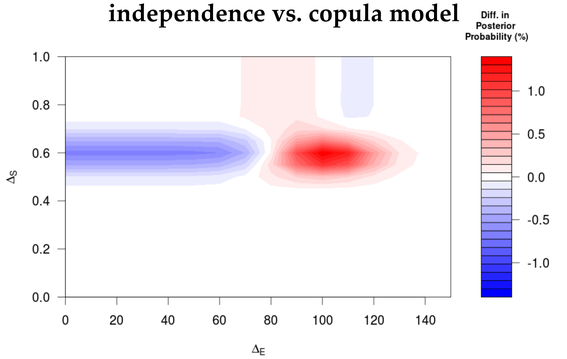
- For the binary efficacy, binary safety scenario, copula model credible interval widths are nearly identical or slightly smaller than separate independent model interval widths over varying levels of treatment group correlation and sample size
- Deviations from the overall pattern described above are observed for certain parameter combinations (pg. 2)
- Similar trends in credible interval width are seen for the continuous efficacy, binary safety scenario (pg. 3)

Probability of Technical Success:

Joint posterior probability of efficacy mean difference greater than Δ_E and adverse event risk difference less than Δ_S

$$Pr(\mu_{trt} - \mu_{pbo} \geq \Delta_E \text{ and } p_{S,trt} - p_{S,pbo} \leq \Delta_S)$$

Difference in POTS for independence vs. copula model



- Difference in mean posterior POTS for continuous-binary bivariate outcome with n=200, $\delta_e = \mu_{trt} - \mu_{pbo} = 100$, $\delta_s = p_{S,trt} - p_{S,pbo} = 0.6$ and $\rho_t = 0.3$
- Red indicates overestimate of POTS by independence model, blue indicates underestimate by independence model

Conclusions:

- The joint copula modeling approach yields posterior credible intervals with nearly identical or slightly smaller width than the independent model approach for most of the parameter combinations examined
- Quantities derived from the joint posterior, such as POTS, are susceptible to estimation errors near true mean or risk difference values when using separate independent models of each outcome

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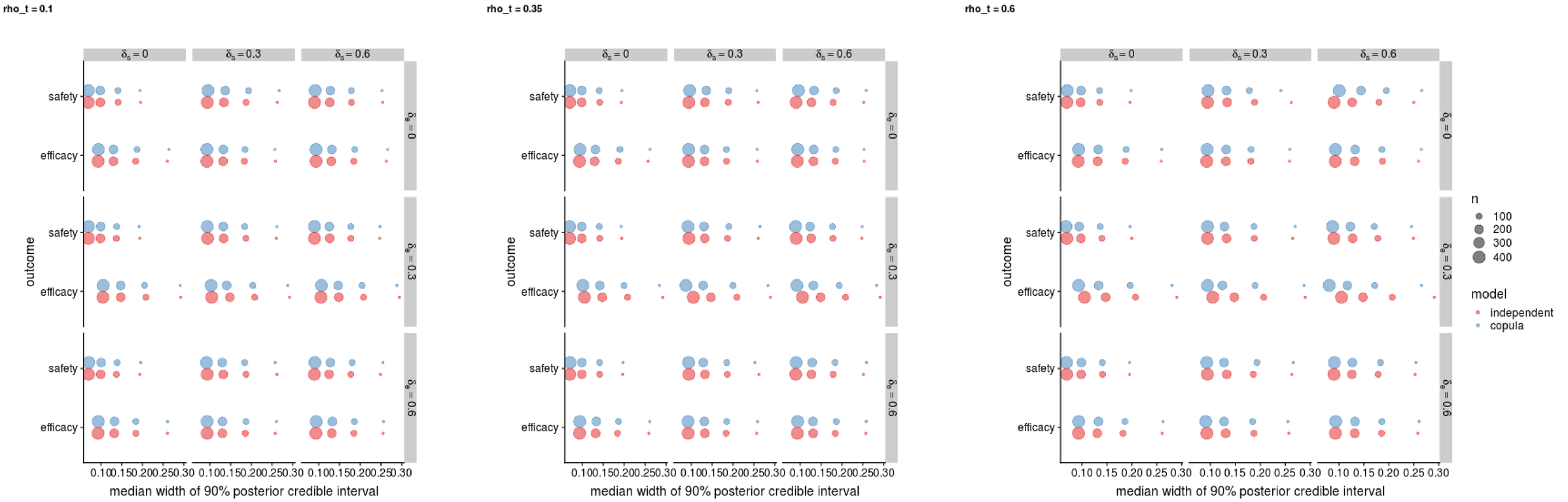
Credible Interval widths for binary efficacy, binary safety outcomes



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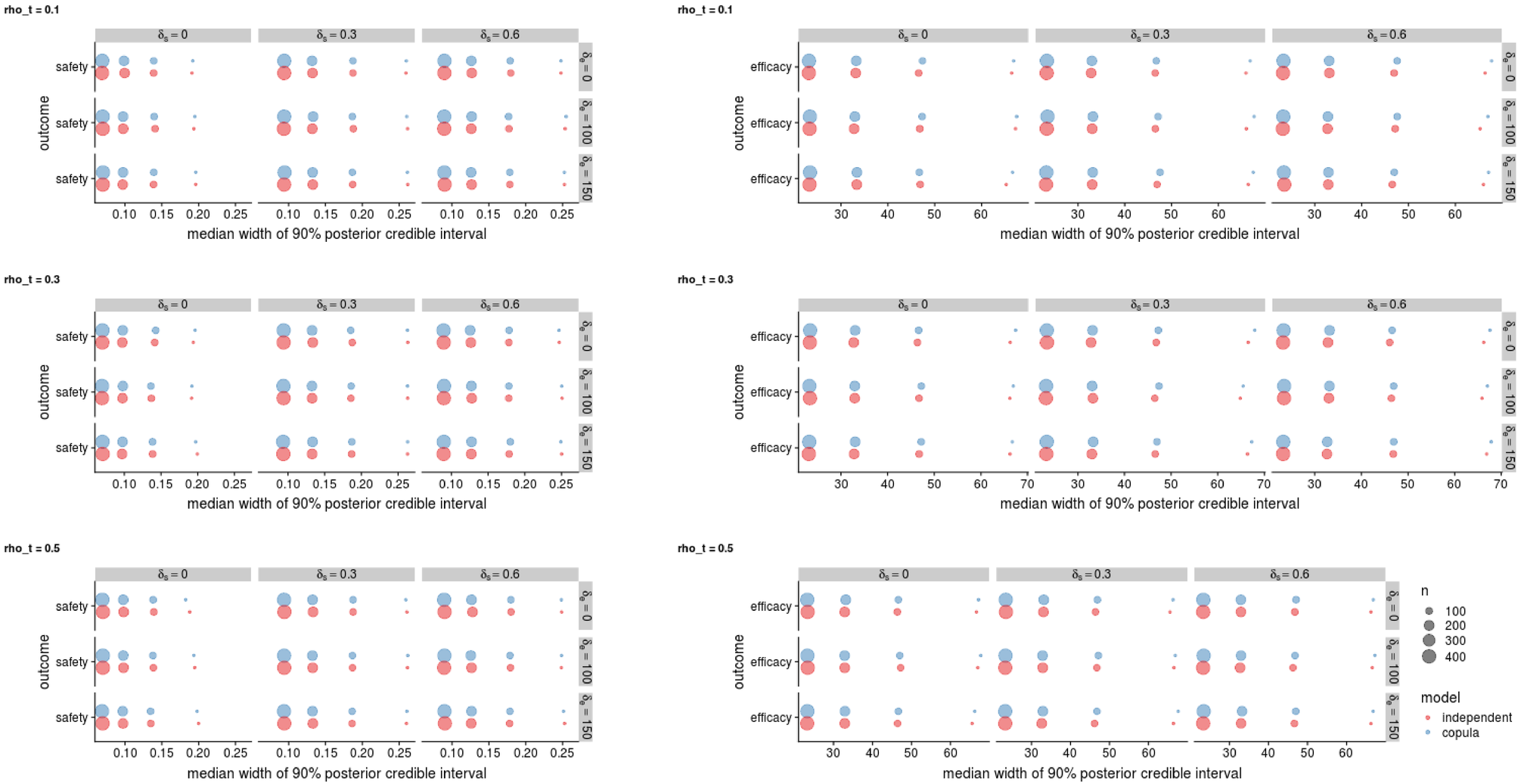
Credible Interval widths for continuous efficacy, binary safety outcomes



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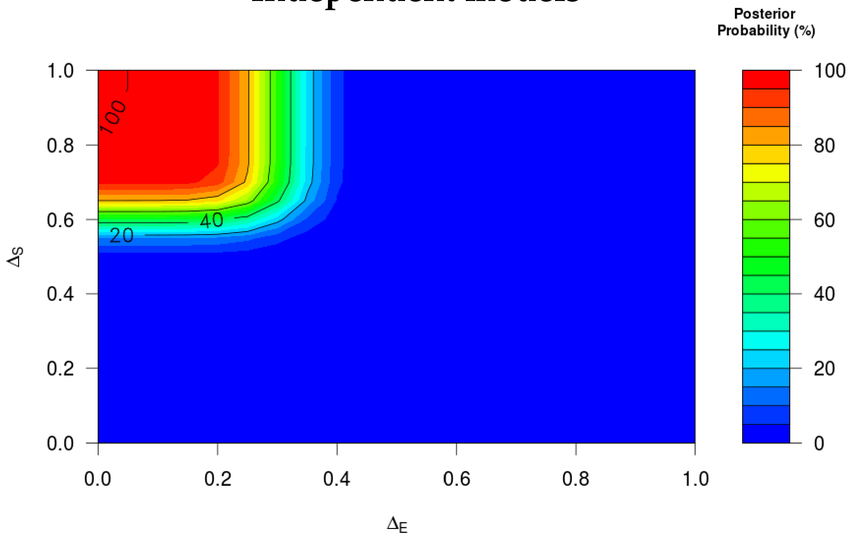
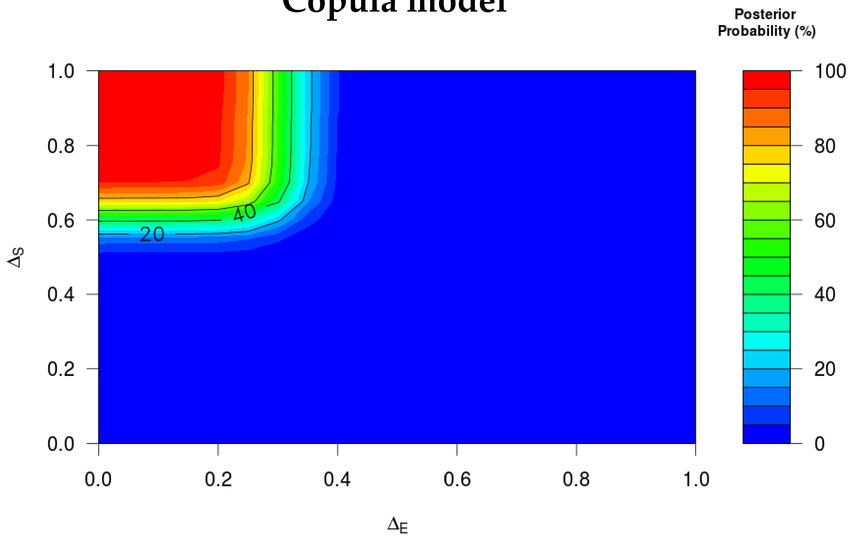
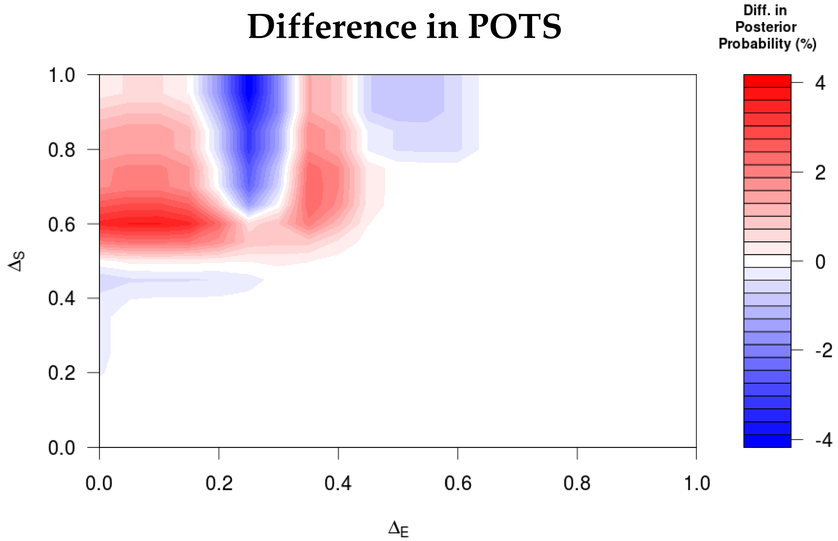
Independent models



Copula model



Difference in POTS



- Representative plot of difference in mean posterior POTS for binary-binary outcome with n=200, $\delta_e = p_{E,trt} - p_{E,pbo} = 0.3$, $\delta_s = p_{S,trt} - p_{S,pbo} = 0.6$ and $\rho_t = 0.35$

- Red indicates overestimate of POTS by independence model, blue indicates underestimate by independence model

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