Bayesian Joint Modelling of Benefit and Risk in Drug Development

Supporting Information

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1.   ADDITIONAL PLOTS AND TABLES FROM SIMULATION STUDIES

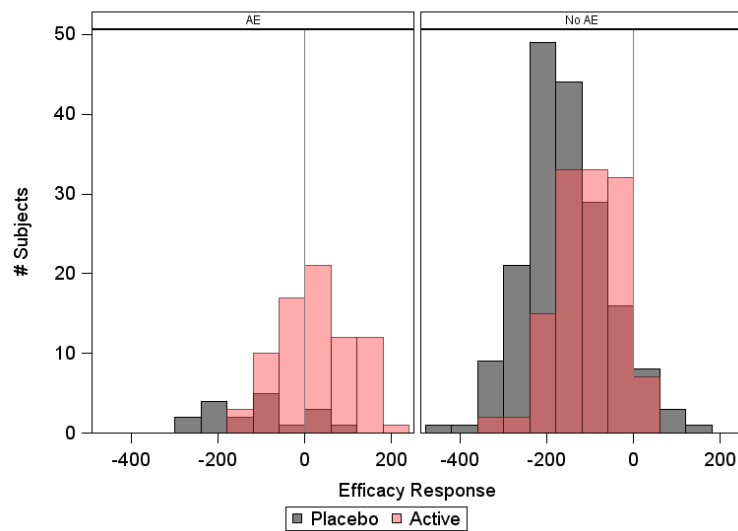## 1.1.   Example 1: Single Efficacy and Safety Responses

Figure 1. Typical simulated dataset for simulation study in Example 1.

1.2.   Example 2: Benefit-Risk and Optimal Dose Selection
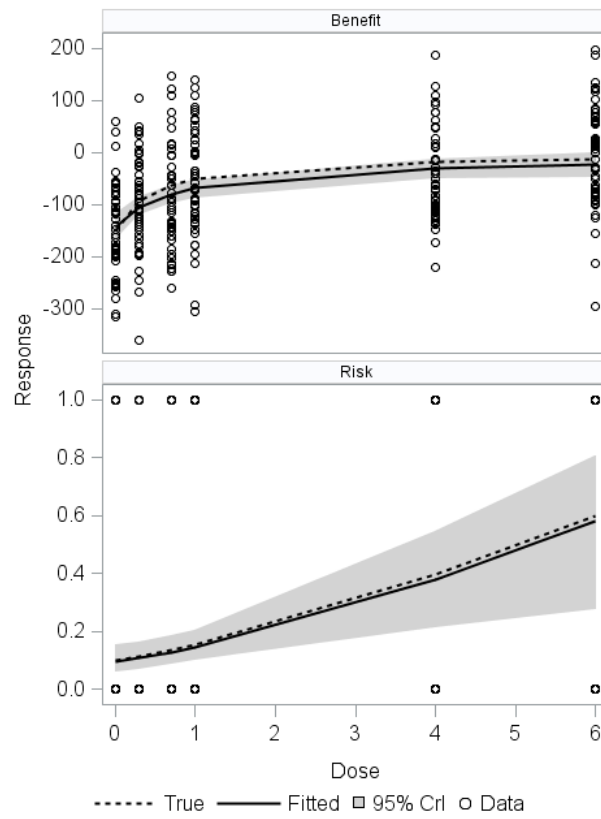

Figure 2. Typical simulated dataset, posterior median curve and 95% credible intervals for simulation study in Example 2.

Table 1. Gaussian copula model parameters averaged across 1000 simulations for Example 2.

	Mean	SD	2.5%	50%	97.5%	Bias	MSE
E_0	-143.74	14.84	-172.59	-143.81	-114.62	-6.26	287.79
E_{max}	157.79	23.46	113.94	156.18	204.47	-7.79	525.60
ED_{50}	1.06	0.77	0.20	0.83	2.60	-0.56	0.89
a	-1.29	0.12	-1.53	-1.29	-1.05	0.01	0.01
b	0.26	0.04	0.19	0.26	0.33	<0.01	<0.01
σ_1	101.94	10.66	82.26	101.04	123.22	-1.94	120.43
σ_2	102.13	10.56	82.60	101.26	123.19	-2.13	111.11
σ_3	102.25	10.58	82.69	101.37	123.39	-2.25	110.49
σ_4	102.23	10.56	82.74	101.36	123.35	-2.23	111.91
σ_5	101.00	10.28	81.97	100.16	121.53	-1.00	94.77
σ_6	100.18	10.11	81.46	99.36	120.35	-0.18	102.02
ρ_1	0.00	0.13	-0.24	0.01	0.25	<0.01	0.02
ρ_2	0.01	0.13	-0.24	0.01	0.26	<0.01	0.02
ρ_3	0.06	0.13	-0.19	0.07	0.31	0.01	0.02
ρ_4	0.11	0.13	-0.14	0.11	0.35	0.01	0.02
ρ_5	0.48	0.09	0.29	0.49	0.64	0.04	0.01
ρ_6	0.59	0.07	0.44	0.60	0.71	0.04	0.01

1.3. Example 3: Single Efficacy and Two Safety Outcomes

Table 2. Copula model parameters averaged across 1000 simulations for the Gaussian and Independence copula models in Example 3.

	Gaussian Copula Model							Independence Copula Model						
	Mean	SD	2.50%	50%	97.50%	Bias	MSE	Mean	SD	2.50%	50%	97.50%	Bias	MSE
DIC	3332.1	34.8	3262.7	3332.7	3400.1	-	-	3435.7	36.2	3361.2	3437.2	3502.6	-	-
μ_1	-150.05	10.1	-169.72	-150.05	-130.47	0.05	100.7	-149.98	10.0	-169.40	-149.99	-130.54	-0.02	101.3
μ_2	-50.30	10.0	-69.65	-50.29	-31.00	0.30	97.94	-49.97	10.0	-69.41	-49.95	-30.59	-0.03	98.30
p_1	0.10	0.03	0.05	0.10	0.16	<0.0	<0.01	0.10	0.03	0.05	0.10	0.16	<0.0	<0.01
p_2	0.40	0.05	0.31	0.40	0.48	<0.0	<0.01	0.40	0.05	0.31	0.40	0.49	<0.0	<0.01
r_1	3.02	0.28	2.49	3.01	3.58	-0.02	0.07	3.01	0.28	2.48	3.00	3.57	-0.01	0.07
r_2	2.00	0.20	1.62	1.99	2.39	<0.0	0.04	2.00	0.21	1.62	1.99	2.41	<0.0	0.04
σ_1	101.57	7.35	87.96	101.14	116.09	-1.57	54.05	100.69	7.23	87.22	100.28	114.92	-0.69	50.59
σ_2	100.13	7.13	86.83	99.72	114.15	-0.13	47.23	100.35	7.21	86.91	99.92	114.52	-0.35	48.49
ω_1	0.55	0.14	0.30	0.54	0.83	-0.05	0.02	0.55	0.14	0.30	0.53	0.82	-0.05	0.02
ω_2	0.54	0.16	0.24	0.52	0.86	-0.04	0.03	0.55	0.17	0.25	0.53	0.89	-0.05	0.03
θ_1^{12}	0.15	0.16	-0.15	0.16	0.45	0.01	0.03	-	-	-	-	-	-	-
θ_1^{13}	0.10	0.10	-0.10	0.10	0.29	0.01	0.01	-	-	-	-	-	-	-
θ_1^{23}	0.44	0.14	0.17	0.45	0.70	0.04	0.02	-	-	-	-	-	-	-
θ_2^{12}	0.74	0.06	0.62	0.75	0.85	0.02	<0.01	-	-	-	-	-	-	-
θ_2^{13}	0.30	0.09	0.12	0.30	0.47	0.03	0.01	-	-	-	-	-	-	-
θ_2^{23}	0.75	0.06	0.63	0.76	0.87	0.03	<0.01	-	-	-	-	-	-	-

Table 3. Posterior probabilities for different clinical thresholds averaged across 1000 simulations for the Gaussian (GCMR) and Independence (ICMR) copula models in Example 3.

E1	S2	Model	S1 < 0.1	S1 < 0.2	S1 < 0.3	S1 < 0.4	S1 < 0.5
60	0.6	ICMR	0.35	4.88	18.42	28.07	29.68
60	0.6	GCMR	0.45	6.97	23.06	29.98	30.48
60	0.7	ICMR	0.50	7.98	33.65	54.82	59.04
60	0.7	GCMR	0.50	9.52	39.46	57.93	59.99
60	0.8	ICMR	0.58	9.70	43.24	73.60	80.50
60	0.8	GCMR	0.51	10.35	48.03	76.92	81.28
60	0.9	ICMR	0.60	10.35	47.39	82.67	91.32
60	0.9	GCMR	0.51	10.54	50.93	85.49	91.80
60	1	ICMR	0.61	10.54	48.73	85.99	95.50
60	1	GCMR	0.51	10.57	51.65	88.41	95.84
80	0.6	ICMR	0.26	3.85	15.20	23.63	25.10
80	0.6	GCMR	0.25	4.84	18.17	24.56	25.05
80	0.7	ICMR	0.37	6.32	27.93	46.54	50.39
80	0.7	GCMR	0.28	6.62	31.37	48.38	50.39
80	0.8	ICMR	0.43	7.70	35.98	62.80	69.13
80	0.8	GCMR	0.29	7.20	38.33	64.94	69.19
80	0.9	ICMR	0.45	8.24	39.53	70.75	78.71
80	0.9	GCMR	0.29	7.33	40.71	72.56	78.71
80	1	ICMR	0.45	8.39	40.69	73.71	82.47
80	1	GCMR	0.29	7.35	41.31	75.20	82.44
100	0.6	ICMR	0.11	1.86	8.07	13.14	14.12
100	0.6	GCMR	0.06	1.81	8.57	12.80	13.21
100	0.7	ICMR	0.16	3.08	14.98	26.24	28.82
100	0.7	GCMR	0.07	2.51	14.92	26.12	27.77
100	0.8	ICMR	0.19	3.79	19.46	35.84	40.13
100	0.8	GCMR	0.07	2.73	18.36	35.86	39.35
100	0.9	ICMR	0.19	4.07	21.46	40.65	46.09
100	0.9	GCMR	0.07	2.78	19.55	40.51	45.55
100	1	ICMR	0.20	4.15	22.12	42.46	48.47
100	1	GCMR	0.07	2.79	19.85	42.14	48.07

2.   ADDITIONAL TABLES FROM REAL DATA EXAMPLE

2.1.   Single Efficacy and Two Safety Outcomes

Table 4. Posterior parameter estimates for the 3-dimensional Gaussian copula model applied to the real data example.

Parameter	Mean	SD	2.5%	50%	97.5%
μ_1	-0.30	0.14	-0.57	-0.30	-0.03
μ_2	0.29	0.12	0.06	0.29	0.52
p_{11}	0.67	0.08	0.51	0.68	0.82
p_{12}	0.92	0.04	0.84	0.93	0.99
p_{21}	0.10	0.05	0.02	0.09	0.20
p_{22}	0.94	0.04	0.87	0.95	1.00
σ_1	0.78	0.10	0.60	0.77	0.99
σ_2	0.74	0.09	0.57	0.73	0.91
$\theta_{Placebo}^{12}$	0.09	0.21	-0.31	0.09	0.50
$\theta_{Placebo}^{13}$	-0.18	0.27	-0.70	-0.19	0.32
$\theta_{Placebo}^{23}$	-0.02	0.29	-0.58	-0.02	0.53
$\theta_{Treatment}^{12}$	-0.30	0.23	-0.73	-0.31	0.15
$\theta_{Treatment}^{13}$	-0.02	0.28	-0.55	-0.03	0.53
$\theta_{Treatment}^{23}$	0.45	0.27	-0.08	0.49	0.92
$\mu_2 - \mu_1$	0.59	0.18	0.22	0.59	0.94
$p_{12} - p_{11}$	0.25	0.09	0.08	0.25	0.43
$p_{22} - p_{21}$	0.84	0.06	0.72	0.85	0.95

3.   GLMM CORRELATION

Recall the GLMM for the single efficacy and safety outcomes scenario,

$$\begin{bmatrix} y_{i1} \\ \Phi^{-1}[P(y_{i2} = 1|u_i)] \end{bmatrix} = \begin{pmatrix} X_i\beta_1 + u_i + \epsilon_i \\ X_i\beta_2{}^* + u_i \end{pmatrix} \quad \epsilon_i \sim N(0, v_i^2) \quad u_i \sim N(0, \tau_i^2), \quad (1)$$

where Φ^{-1} in (1) is the inverse of the standard normal cumulative distribution function (CDF). For simplicity, the mean of both responses y_{i1} and y_{i2} are assumed to depend on the same set of covariates X_i. However, the parameters modulating this relationship, β_1 and β_2, are allowed to differ. In this case, the correlation between y_{i1} and y_{i2} can be estimated as[1]:

$$\rho_i = \text{Corr}\,(y_{i1}, y_{i2}) = \left(\frac{\tau_i^2}{1 + \tau_i^2}\right) \frac{\phi\left(\frac{X_i\beta_2{}^*}{\sqrt{1 + \tau_i^2}}\right)}{\sqrt{\Phi\left(\frac{X_i\beta_2{}^*}{\sqrt{1 + \tau_i^2}}\right)\left\{1 - \Phi\left(\frac{X_i\beta_2{}^*}{\sqrt{1 + \tau_i^2}}\right)\right\}}}, \quad (2)$$

where ϕ and Φ are the density and cumulative distribution functions of the standard normal distribution, respectively. The expression in (2) implies a positive correlation between y_{i1} and y_{i2}. To achieve negative correlation the continuous response y_{i1} should be changed to $-y_{i1}$ together with the interpretation of the fixed effect parameters in (1). In practice, ρ_i is a parameter which should be accounted for when making inference but is not the primary purpose of the analysis and can be seen as a nuisance parameter.

4.   GLMM LOGISTIC MODEL

If the binary response y_{i2} in (1) is modelled using a logistic regression instead, marginal effects can be obtained using the approximation $\beta_2 \approx \beta_2{}^* / \sqrt{1 + 0.346\ \tau_i^2}$ [2].

5.   COPULA LIKELIHOOD DERIVATION

A copula function $C[u, v|\theta]$ with cumulative probabilities u and v has the following properties:

$$
\begin{array}{lll}
C[u, 0|\theta] = C[0, v|\theta] = C[0,0|\theta] & = 0 & (C1) \\
C[u, 1|\theta] & = u & (C2) \\
C[1, v|\theta] & = v & (C3) \\
C[1,1|\theta] & = 1 & (C4)
\end{array}
$$

5.1.   Gaussian Copula Model for Example 1: Single Efficacy and Safety Responses

Example 1 contains one continuous normal distributed variable and one binary Bernoulli distributed response variable. Therefore, for the i-th individual,

$$
y_{i1} \sim N(\mu_i, \sigma_i), \quad y_{i2} \sim Bernoulli(p_i) .
$$

The following model is assumed for the mean, dispersion and dependence parameters:

$$
\begin{bmatrix} \mu_i \\ \Phi^{-1}(p_i) \end{bmatrix} = \begin{pmatrix} x_{i1}\,\beta_{11} + x_{i2}\,\beta_{12} \\ x_{i1}\,\beta_{21} + x_{i2}\,\beta_{22} \end{pmatrix} \quad \sigma_i = x_{i1}s_1 + x_{i2}\,s_2 \quad \theta_{12} = x_{i1}\omega_1^{12} + x_{i2}\omega_2^{12},
$$

where:
- x_{it} is the design matrix for subject i, represented by indicator variables for whether the subject is on treatment t.
- β_{jt} are the treatment effect parameters for the normal mean and binary probability.
- s_t is the normal dispersion parameter for treatment t.
- ω_t^{12} is the copula dependence parameter between responses y_1 and y_2 for treatment t.

The joint cumulative distribution function for the selected copula is easily obtained using the model for the means, dispersion and dependence parameters combined with the marginal distribution functions and the copula $C(\cdot, \cdot | \theta)$ to create a joint CDF as:

$$
F_{12}(y_{i1}, y_{i2}| \theta_{12}) = C[F_1(y_{i1}| \mu_i, \sigma_i), F_2(y_{i2}|p_i)|\theta_{12}].
$$

This is not very practical for model fitting and therefore the likelihood for the joint density-mass function is derived by taking the partial derivative of the continuous variable and performing finite differencing of the resulting function to get the discrete mass. Taking the partial derivative gives:

$$
\frac{\partial}{\partial y_{i1}} F_{12}(y_{i1}, y_{i2}| \theta_{12}) = \frac{\partial}{\partial F_1(y_{i1})} C[F_1(y_{i1}| \mu_i, \sigma_i), F_2(y_{i2}|p_i)| \theta_{12}] \cdot \frac{d}{dy_{i1}} F_1(y_{i1}).
$$

Therefore,

$$\frac{\partial}{\partial y_{i1}} F_{12}(y_{i1}, y_{i2}| \theta_{12}) = \frac{\partial}{\partial F_1(y_{i1})} C[F_1(y_{i1}| \mu_i, \sigma_i), F_2(y_{i2}|p_i)| \theta_{12}] f_1(y_{i1}|\mu_i, \sigma_i). \quad (3)$$

Using (3) and taking the finite difference evaluated at $F_2(y_{i2}|p_i)$ and $F_2(y_{i2} - 1|p_i)$ gives the joint mass function,

$$f_{12}(y_{i1}, y_{i2}| \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \left\{ \frac{\partial}{\partial F_1(y_{i1})} C[F_1(y_{i1}| \mu_i, \sigma_i), F_2(y_{i2}|p_i)| \theta_{12}] - \frac{\partial}{\partial F_1(y_{i1})} C[F_1(y_{i1}| \mu_i, \sigma_i), F_2(y_{i2} - 1|p_i)|\theta_{12}] \right\}, \quad (4)$$

where:

- $f_1(y_{i1}|\mu_i, \sigma_i)$ is the normal density function for y_{i1} with mean μ_i and dispersion σ_i.
- $F_1(y_{i1}| \mu_i, \sigma_i)$ is the normal CDF for y_{i1} with mean μ_i and dispersion σ_i.
- $F_2(y_{i2}|p_i)$ is the Bernoulli CDF for y_{i2} with $p_i = P(y_{i2} = 1)$.
- $F_2(y_{i2} - 1|p_i)$ is the Bernoulli CDF for $(y_{i2} - 1)$ with $P(y_{i2} = 1)$ denoted p_i.
- θ_{12} is the copula dependence parameter.

The density mass function in (4) is a generic function for the joint likelihood of normal and Bernoulli distributed data with dependence modelled via the chosen copula function $C[\cdot, \cdot |\theta_{12}]$. For the Gaussian copula, it can be shown[3] that the partial derivative is:

$$\frac{\partial}{\partial F_1(y_{i1})} C[F_1(y_{i1}| \mu_i, \sigma_i), F_2(y_{i2}|p_i)| \theta_{12}] = \Phi\left(\frac{\Phi^{-1}[F_2(y_{i2}|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}| \mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}} \right).$$

Therefore,

$$f_{12}(y_{i1}, y_{i2}| \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \left\{ \Phi\left(\frac{\Phi^{-1}[F_2(y_{i2}|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}| \mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}} \right) - \Phi\left(\frac{\Phi^{-1}[F_2(y_{i2}-1|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}| \mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}} \right) \right\}. \quad (5)$$

The expression in (5) can be simplified by considering the CDF for the Bernoulli distribution:

$$F_2(y_{i2}|p_i) = \begin{cases} 0 & : & y_{i2} < 0 \\ 1 - p_i & : & 0 \le y_{i2} < 1 \, . \\ 1 & : & y_{i2} \ge 1 \end{cases} \quad (6)$$

Therefore, when $y_{i2} = 0$, the joint mass function becomes:

$$f_{12}(y_{i1}, y_{i2}|\ \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \left\{ \Phi\left(\frac{\Phi^{-1}[F_2(0|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) - \Phi\left(\frac{\Phi^{-1}[F_2(-1|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) \right\}.$$

Using (6) the mass function can be written as:

$$f_{12}(y_{i1}, y_{i2}|\ \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \left\{ \Phi\left(\frac{\Phi^{-1}[1-p_i] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) - \Phi\left(\frac{\Phi^{-1}[0] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) \right\}.$$

Since the inverse of the standard normal CDF evaluated at zero is $-\infty$, the mass function simplifies to,

$$f_{12}(y_{i1}, y_{i2}|\ \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \left\{ \Phi\left(\frac{\Phi^{-1}[1-p_i] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) \right\}.$$

When $y_{i2} = 1$, the joint mass function becomes:

$$f_{12}(y_{i1}, y_{i2}|\ \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \left\{ \Phi\left(\frac{\Phi^{-1}[F_2(1|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) - \Phi\left(\frac{\Phi^{-1}[F_2(0|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) \right\}.$$

Using (6) the mass function becomes:

$$f_{12}(y_{i1}, y_{i2}|\ \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \left\{ \Phi\left(\frac{\Phi^{-1}[1] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) - \Phi\left(\frac{\Phi^{-1}[1-p_{i2}] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) \right\},$$

Since the inverse of the standard normal CDF evaluated at unity is ∞, the mass function simplifies to

$$f_{12}(y_{i1}, y_{i2}|\ \theta_{12}) = f_1(y_{i1}|\mu_i, \sigma_i) \cdot \left\{ 1 - \Phi\left(\frac{\Phi^{-1}[1-p_{i2}] - \theta_{12}\cdot\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1 - \theta_{12}^2}} \right) \right\}.$$

Therefore, the joint mass function for a normal and Bernoulli distributions combined via the Gaussian copula is:

$$f_{12}(y_{i1}, y_{i2} | \ \theta_{12}) = \begin{cases} f_1(y_{i1}|\mu_i, \sigma_i) \cdot \left\{ \Phi\left(\dfrac{\Phi^{-1}[1-p_i]- \ \theta_{12}\cdot\Phi^{-1}[F_1(y_{i1}| \ \mu_i,\sigma_i)]}{\sqrt{1- \theta_{12}^2}} \right) \right\} & : y_{i2} = 0 \\[2em] f_1(y_{i1}|\mu_i, \sigma_i) \cdot \left\{ 1 - \ \Phi\left(\dfrac{\Phi^{-1}[1-p_{i2}]- \ \theta_{12}\cdot\Phi^{-1}[F_1(y_{i1}| \ \mu_i,\sigma_i)]}{\sqrt{1- \theta_{12}^2}} \right) \right\} & : y_{i2} = 1 \end{cases} \qquad (7)$$

The joint mass function in (7) can be used to build the likelihood for the model parameters given data y_{i1} and y_{i2}.

5.2. Gaussian Copula Model for Example 2: Benefit-Risk and Optimal Dose Selection

In simulated example 2 the responses are still normal and binary. However, the mean of the normal distribution is now a 3-parameter Emax model, and the model for the dispersion and dependence parameters are also changed to allow for separate parameters for each dose d as follows,

$$\begin{bmatrix} \mu_{1i} \\ \Phi^{-1}(p_i) \end{bmatrix} = \begin{pmatrix} \mathrm{E}_0 + \dfrac{\mathrm{E}_{\max}d}{\mathrm{ED}_{50} + d} \\ a + b \, d \end{pmatrix},$$
$$\sigma_i = s_d \,,$$
$$\theta_{12} = \omega_d \,.$$

Apart from the change in the model for the normal mean, the likelihood derivation is identical to that in Section 4.1 for Example 1.

5.3. Gaussian and Independence Copula Models for Example 3: Single Efficacy and Two Safety Outcomes

5.3.1. Gaussian Copula Joint Likelihood

Example 3 contains one continuous normal distributed variable, one binary Bernoulli distributed variable and one count Negative Binomial distributed variable:

$$y_{i1} \sim N(\mu_i, \sigma_i) \quad y_{i2} \sim Bernoulli(p_i) \quad y_{i3} \sim Negative\ Binomial(r_i, \varphi_i)$$

The models for means, dispersions and dependence parameters are:

$$\begin{bmatrix} \mu_i \\ \Phi^{-1}(p_i) \\ log(r_i) \end{bmatrix} = \begin{pmatrix} x_{i1}\,\beta_{11} + x_{i2}\,\beta_{12} \\ x_{i1}\,\beta_{21} + x_{i2}\,\beta_{22} \\ x_{i1}\,\beta_{31} + x_{i2}\,\beta_{32} \end{pmatrix} \qquad \begin{bmatrix} \sigma_i \\ \varphi_i \end{bmatrix} = \begin{pmatrix} x_{i1}s_{11} + x_{i2}\,s_{12} \\ x_{i1}s_{31} + x_{i2}\,s_{32} \end{pmatrix} \qquad \begin{bmatrix} \theta_{12} \\ \theta_{13} \\ \theta_{23} \end{bmatrix} = \begin{pmatrix} x_{i1}\omega_1^{12} + x_{i2}\omega_2^{12} \\ x_{i1}\omega_1^{13} + x_{i2}\omega_2^{13} \\ x_{i1}\omega_1^{23} + x_{i2}\omega_1^{23} \end{pmatrix},$$

where:

- x_{it} is the design matrix component for subject i, defined as an indicator variables for whether the subject is on treatment t.
- β_{jt} are the treatment effect parameters for the normal mean, binary probability, and negative binomial rate.
- s_{jt} is the dispersion parameter for the j-th measure for treatment t (note that the Bernoulli distribution does not have a dispersion parameter).
- ω_t^{jk} are the copula dependence parameters between responses y_j and y_k for treatment t.

The models for the mean, dispersion and dependence parameter vector are combined with the marginal distributions functions and the Gaussian copula $C^{Gauss}(\cdot, \cdot, \cdot \mid \boldsymbol{\theta})$ to create the copula CDF as:

$$F_{123}(y_{i1}, y_{i2}, y_{i3} \mid \boldsymbol{\theta}) = C^{Gauss}[\, F_1(y_{i1} \mid \mu_i, \sigma_i),\ F_2(y_{i2} \mid p_i),\ F_3(y_{i3} \mid r_i, \varphi_i) \mid \boldsymbol{\theta}].$$

In order to derive the joint density-mass function the partial derivative with respect to the continuous variable y_{i1} is calculated:

$$\frac{\partial}{\partial y_{i1}} F_{123}(y_{i1}, y_{i2}, y_{i3} \mid \boldsymbol{\theta}) = \frac{\partial}{\partial F_1(y_{i1})} C^{Gauss}[\, F_1(y_{i1} \mid \mu_i, \sigma_i),\ F_2(y_{i2} \mid p_i),\ F_3(y_{i3} \mid r_i, \varphi_i) \mid \boldsymbol{\theta}] \cdot \frac{d}{dy_{i1}} F_1(y_{i1}).$$

Therefore,

$$\frac{\partial}{\partial y_{i1}} F_{123}(y_{i1}, y_{i2}, y_{i3} \mid \boldsymbol{\theta}) = \frac{\partial}{\partial F_1(y_{i1})} C^{Gauss}[\, F_1(y_{i1} \mid \mu_i, \sigma_i),\ F_2(y_{i2} \mid p_i),\ F_3(y_{i3} \mid r_i, \varphi_i) \mid \boldsymbol{\theta}]\, f_1(y_{i1} \mid \mu_i, \sigma_i). \qquad (8)$$

The work by de Leon [2] shows that due to the elliptical nature of the Gaussian copula the partial derivative in (8) with respect to $F_1(y_{i1})$ for the 3-dimensional Gaussian Copula Distribution Function is the same as the 2-dimensional Gaussian Copula Distribution Function for $F_2(y_{i2})$ and $F_3(y_{i3})$ conditional on $F_1(y_{i1})$, i.e.,

$$\frac{\partial}{\partial y_{i1}} F_{123}(y_{i1}, y_{i2}, y_{i3} | \boldsymbol{\theta}) = C^{Gauss}\left[F_{2|1}(y_{i2}|y_{i1}), F_{3|1}(y_{i3}|y_{i1}) | \theta_{23|1}\right] f_1(y_{i1}|\mu_i, \sigma_i),$$

where:

$$F_{2|1}(y_{i2}|y_{i1}) = \Phi\left(\frac{\Phi^{-1}[F_2(y_{i2}|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{12}^2}}\right),$$

$$F_{3|1}(y_{i3}|y_{i1}) = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3}|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{13}^2}}\right).$$

Pair-wise finite differencing can then be carried out to achieve the full joint density mass function for y_{i1}, y_{i2} and y_{i3}. The following notation will be used: $F_{j_1|j_2}^+ = F_{j_1|j_2}(y_{ij_1}|y_{ij_2})$ and $F_{j_1|j_2}^- = F_{j_1|j_2}(y_{ij_1} - 1|y_{ij_2})$. The joint density mass function is:

$$f_{123}(y_{i1}, y_{i2}, y_{i3}|\boldsymbol{\theta}) = f_1(y_{i1}|\mu_i, \sigma_i)\{C^{Gauss}[F_{2|1}^+, F_{3|1}^+|\theta_{23|1}] - C^{Gauss}[F_{2|1}^+, F_{3|1}^-|\theta_{23|1}]$$
$$-C^{Gauss}[F_{2|1}^-, F_{3|1}^+|\theta_{23|1}] + C^{Gauss}[F_{2|1}^-, F_{3|1}^-|\theta_{23|1}]\}, \qquad (9)$$

with:

$$F_{2|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_2(y_{i2}|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{12}^2}}\right) \qquad F_{2|1}^- = \Phi\left(\frac{\Phi^{-1}[F_2(y_{i2} - 1|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{12}^2}}\right),$$

$$F_{3|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3}|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{13}^2}}\right) \qquad F_{3|1}^- = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3} - 1|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{13}^2}}\right).$$

This general formula for the joint density mass function can be simplified using properties of copulas and the marginal distributions as described below.

When $y_{i2} = 0$ and $y_{i3} = 0$ the conditional values are:

$$F_{2|1}^+ = \Phi\left(\frac{\Phi^{-1}[(1-p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right) \qquad F_{2|1}^- = \Phi\left(\frac{\Phi^{-1}[0] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right) = 0$$

$$F_{3|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_3(0|r_i,\varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{13}^2}}\right) \qquad F_{3|1}^- = \Phi\left(\frac{\Phi^{-1}[F_3(-1|r_i,\varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{13}^2}}\right) = 0$$

This means any of the copula terms in (9) with $F_{2|1}^-$ or $F_{3|1}^-$ become zero by property (C1) and the resulting likelihood is:

$$f_{123}(y_{i1},y_{i2},y_{i3}|\boldsymbol{\theta}) = f_1(y_{i1}|\mu_i,\sigma_i)\left\{C^{Gauss}\left[F_{2|1}^+,F_{3|1}^+|\theta_{23|1}\right]\right\}.$$

When $y_{i2} = 0$ and $y_{i3} > 0$ the conditional values are:

$$F_{2|1}^+ = \Phi\left(\frac{\Phi^{-1}[(1-p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right) \qquad F_{2|1}^- = \Phi\left(\frac{\Phi^{-1}[F_2(-1|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right) = 0,$$

$$F_{3|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3}|r_i,\varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{13}^2}}\right) \qquad F_{3|1}^- = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3}-1|r_i,\varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{13}^2}}\right).$$

This means any of the copula terms in (9) with $F_{2|1}^-$ become zero by property (C1) and the resulting likelihood is:

$$f_{123}(y_{i1},y_{i2},y_{i3}|\boldsymbol{\theta}) = f_1(y_{i1}|\mu_i,\sigma_i)\cdot\left\{C^{Gauss}\left[F_{2|1}^+,F_{3|1}^+|\theta_{23|1}\right] - C^{Gauss}\left[F_{2|1}^+,F_{3|1}^-|\theta_{23|1}\right]\right\}.$$

When $y_{i2} = 1$ and $y_{i3} = 0$ the conditional values are:

$$F_{2|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_2(1|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{12}^2}}\right) = 1 \qquad F_{2|1}^- = \Phi\left(\frac{\Phi^{-1}[(1 - p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{12}^2}}\right),$$

$$F_{3|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_3(0|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{13}^2}}\right) \qquad F_{3|1}^- = \Phi\left(\frac{\Phi^{-1}[F_3(-1|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{13}^2}}\right) = 0 \, .$$

This means any of the copula terms in (9) with $F_{3|1}^-$ become zero by property (C1) and by (C3) the remaining copula terms with $F_{2|1}^+$ resolve to the conditional CDF value it is paired with, i.e., $C^{Gauss}[F_{2|1}^+, F_{3|1}^+|\theta_{23|1}] = F_{3|1}^+$ and the likelihood becomes:

$$f_{123}(y_{i1}, y_{i2}, y_{i3}|\boldsymbol{\theta}) = f_1(y_{i1}|\mu_i, \sigma_i)\left\{F_{3|1}^+ - C^{Gauss}[F_{2|1}^-, F_{3|1}^+|\theta_{23|1}]\right\}.$$

When $y_{i2} = 1$ and $y_{i3} > 0$ the conditional values are:

$$F_{2|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_2(1|p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{12}^2}}\right) = 1 \qquad F_{2|1}^- = \Phi\left(\frac{\Phi^{-1}[(1 - p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{12}^2}}\right),$$

$$F_{3|1}^+ = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3}|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{13}^2}}\right) \qquad F_{3|1}^- = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3} - 1|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1 - \theta_{13}^2}}\right).$$

This means none of the copula terms in (9) become zero but copula terms with $F_{2|1}^+$ resolve to the CDF value it is paired with, i.e., $C^{Gauss}[F_{2|1}^+, F_{3|1}^+|\theta_{23|1}] = F_{3|1}^+$ and the likelihood becomes:

$$f_{123}(y_{i1}, y_{i2}, y_{i3}|\boldsymbol{\theta}) = f_1(y_{i1}|\mu_i, \sigma_i)\left\{F_{3|1}^+ - F_{3|1}^- - C^{Gauss}[F_{2|1}^-, F_{3|1}^+|\theta_{23|1}] + C^{Gauss}[F_{2|1}^-, F_{3|1}^-|\theta_{23|1}]\right\}.$$

Therefore, the joint likelihood function is well defined for each set of y_{i1}, y_{i2} and y_{i3}. It is also possible to see that, for the cases when $y_{i2} = 0$ and $y_{i2} = 1$, the conditional distribution functions for $F_{2|1}^+$ and $F_{2|1}^-$ are in fact the same, i.e.,

$$F_{2|1}^{+} = \Phi\left(\frac{\Phi^{-1}[(1-p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right) \quad : y_{i2} = 0\,,$$

$$F_{2|1}^{-} = \Phi\left(\frac{\Phi^{-1}[(1-p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right) \quad : y_{i2} = 1\,.$$

This implies that the likelihood function can be further simplified to a single calculation for $F_{2|1}$. Therefore, the joint likelihood function for parameters $\boldsymbol{\Omega} = (\mu_i, \sigma_i, p_i, r_i, \varphi_i, \theta_{12}, \theta_{13}, \theta_{23|1})$ in a Gaussian Copula Regression model for normal, binary and negative binomial response data $\boldsymbol{y} = (y_{i1}, y_{i2}, y_{i3})$ simplifies to:

$$L(\boldsymbol{\Omega}|\boldsymbol{y}) = \begin{cases} f_1(y_{i1}|\mu_i, \sigma_i)\left\{C^{Gauss}\left[F_{2|1}, F_{3|1}^{+}|\theta_{23|1}\right]\right\} & : y_{i2} = 0 \quad y_{i3} = 0 \\ f_1(y_{i1}|\mu_i, \sigma_i)\left\{C^{Gauss}\left[F_{2|1}, F_{3|1}^{+}|\theta_{23|1}\right] - C^{Gauss}\left[F_{2|1}, F_{3|1}^{-}|\theta_{23|1}\right]\right\} & : y_{i2} = 0 \quad y_{i3} > 0 \\ f_1(y_{i1}|\mu_i, \sigma_i)\left\{F_{3|1}^{+} - C^{Gauss}\left[F_{2|1}, F_{3|1}^{+}|\theta_{23|1}\right]\right\} & : y_{i2} = 1 \quad y_{i3} = 0 \\ f_1(y_{i1}|\mu_i, \sigma_i)\left\{F_{3|1}^{+} - F_{3|1}^{-} - C^{Gauss}\left[F_{2|1}, F_{3|1}^{+}|\theta_{23|1}\right] + C^{Gauss}\left[F_{2|1}, F_{3|1}^{-}|\theta_{23|1}\right]\right\} & : y_{i2} = 1 \quad y_{i3} > 0 \end{cases}$$

where:

$$F_{2|1} = \Phi\left(\frac{\Phi^{-1}[(1-p_i)] - \theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right),$$

$$F_{3|1}^{+} = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3}|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1-\theta_{13}^2}}\right) \quad \text{and} \quad F_{3|1}^{-} = \Phi\left(\frac{\Phi^{-1}[F_3(y_{i3}-1|r_i, \varphi_i)] - \theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i, \sigma_i)]}{\sqrt{1-\theta_{13}^2}}\right),$$

and:

- θ_{12} is the copula dependence parameter for y_1 and y_2.
- θ_{13} is the copula dependence parameter for y_1 and y_3.
- $\theta_{23|1}$ is the copula dependence parameter for y_2 and y_3 conditional on y_1.
- $C^{Gauss}[\,\cdot\,,\,\cdot\,|\,\theta\,]$ is the bivariate Gauss copula distribution function.

Following the work by de Leon [2] it is also possible to obtain estimates of the unconditional dependency parameter θ_{23} using the following relation,

$$\theta_{23} = \left(\theta_{23|1}\sqrt{1-\theta_{12}^2}\sqrt{1-\theta_{13}^2}\right) + (\theta_{12}\theta_{13})\,.$$

5.3.2. Independence Copula Joint Likelihood

It is relatively straightforward to show that the joint likelihood for parameters $\Omega = (\mu_i, \varphi_i, p_i, r_i, \varphi_i)$ in an Independence Copula Regression model for normal, binary and negative binomial response data $y = (y_{i1}, y_{i2}, y_{i3})$ simplifies to:

$$L(\Omega|y) = f_1(y_{i1}|\mu_i, \varphi_i)f_2(y_{i2}|p_i)f_3(y_{i3}|r_i, \varphi_i) ,$$

where f_1, f_2 and f_3 are the marginal density or mass functions for y_{i1}, y_{i2} and y_{i3}, respectively.

5.4. Real Data Example: Single Efficacy and Two Safety Outcomes

The 3-dimensional real data example contains one continuous variable assumed to follow a normal distribution, and two binary variables assumed to follow a Bernoulli distribution,

$$y_{i1} \sim N(\mu_i, \sigma_i), \quad y_{i2} \sim Bernoulli(p_{i1}), \quad y_{i3} \sim Bernoulli(p_{i2}).$$

The models for the mean, dispersion and dependence parameters are:

$$\begin{bmatrix} \mu_i \\ \Phi^{-1}(p_{i1}) \\ \Phi^{-1}(p_{i2}) \end{bmatrix} = \begin{pmatrix} x_{i1}\,\beta_{11} + x_{i2}\,\beta_{12} + x_{i3}\,\beta_{13} \\ x_{i1}\,\beta_{21} + x_{i2}\,\beta_{22} \\ x_{i1}\,\beta_{31} + x_{i2}\,\beta_{32} \end{pmatrix} \qquad \sigma_i = x_{i1}s_1 + x_{i2}\,s_2 \qquad \begin{bmatrix} \theta_{12} \\ \theta_{13} \\ \theta_{23} \end{bmatrix} = \begin{pmatrix} x_{i1}\omega_1^{12} + x_{i2}\omega_2^{12} \\ x_{i1}\omega_1^{13} + x_{i2}\omega_2^{13} \\ x_{i1}\omega_1^{23} + x_{i2}\omega_1^{23} \end{pmatrix},$$

where:

- x_{im} is the design matrix component for the m-th covariate for the i-th subject: x_{i1} and x_{i2} are indicator variables for treatment $t = 1$ and $t = 2$, respectively, and x_{i3} is the baseline value of C-peptide levels.
- β_{jm} are the covariate effect parameters for the normal mean and binary probabilities.
- s_t is the normal dispersion parameter for treatment t (recall that the Bernoulli distribution does not have a dispersion parameter).
- ω_t^{jk} are the copula dependence parameter between responses y_j and y_k for treatment t.

Derivation of the likelihood function follows the same process as in the simulated Example 3 described in Section 4.3. The partial derivative of the continuous response is obtained and then pair-wise finite differencing is performed for the two discrete responses. After this has been derived the properties of the Bernoulli margins are applied and the function is simplified for each combination of possible values. The resulting likelihood function is:

$$
L(\boldsymbol{\Omega}|\boldsymbol{y}) = \begin{cases}
f_1(y_{i1}|\mu_i,\sigma_i)\left\{C^{Gauss}\left[F_{2|1},F_{3|1}|\theta_{23|1}\right]\right\} & : y_{i2}=0 \quad y_{i3}=0 \\
f_1(y_{i1}|\mu_i,\sigma_i)\left\{F_{2|1}-C^{Gauss}\left[F_{2|1},F_{3|1}|\theta_{23|1}\right]\right\} & : y_{i2}=0 \quad y_{i3}=1 \\
f_1(y_{i1}|\mu_i,\sigma_i)\left\{F_{3|1}-C^{Gauss}\left[F_{2|1},F_{3|1}|\theta_{23|1}\right]\right\} & : y_{i2}=1 \quad y_{i3}=0 \\
f_1(y_{i1}|\mu_i,\sigma_i)\left\{1-F_{2|1}-F_{3|1}+C^{Gauss}\left[F_{2|1},F_{3|1}|\theta_{23|1}\right]\right\} & : y_{i2}=1 \quad y_{i3}=1
\end{cases},
$$

where:

$$
F_{2|1} = \Phi\left(\frac{\Phi^{-1}[(1-p_{i1})]-\theta_{12}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{12}^2}}\right) \quad F_{3|1} = \Phi\left(\frac{\Phi^{-1}[(1-p_{i2})]-\theta_{13}\Phi^{-1}[F_1(y_{i1}|\mu_i,\sigma_i)]}{\sqrt{1-\theta_{13}^2}}\right).
$$

6.   MCMC SPECIFICATIONS AND MONTE CARLO ERROR

6.1.   Example 1

For both models in Example 1, the 1000 simulated datasets were split into 4 groups with 100 datasets for the initial group and 300 for each of the other three groups. The grouped datasets were then run with identical programs with different starting seeds (details below).

MCMC Characteristic	Values Used
Random Seed	G1=12345678, G2=87654321, G3=5678, G4=1234
Burn in	5000
Chain Length	400000
Chain Thinning	40
Tuning Loops	3000
Prior Distributions	$\beta_{jt} \sim Normal\,(0, SD = 1000)$ $\upsilon_t, \tau_t, \sigma_t \sim Inv.\,Gamma\,(shape = 0.001, scale = 0.001)$ $\theta_t \sim Uniform[-1,1]$

Table 5. Monte Carlo Standard Error (MCSE) and ratio to the estimated Standard Deviation (SD) of the posterior distribution (mean value across all 1000 datasets).

	GLMM Model			Gaussian Copula Model		
	MCSE	SD	MCSE/SD	MCSE	SD	MCSE/SD
μ_1	0.11	10.10	0.01	0.12	10.13	0.01
μ_2	0.17	10.11	0.02	0.14	10.04	0.01
p_1	<0.01	0.03	0.01	<0.01	0.03	0.01
p_2	<0.01	0.05	0.02	<0.01	0.05	0.01
ρ_1	0.01	0.07	0.12	<0.01	0.09	0.01
ρ_2	<0.01	0.05	0.09	<0.01	0.05	0.01
θ_1	-	-	-	<0.01	0.16	0.01
θ_2	-	-	-	<0.01	0.07	0.01

6.2.   Example 2

For both models in Example 2, the 1000 datasets were split into 4 groups with 100 datasets for the initial group and 300 for each of the other three groups. The grouped datasets were then run with identical programs with different starting seeds (details below).

MCMC Characteristic	Values Used
Random Seed Burn in Chain Length Chain Thinning Tuning Loops	G1=12345678, G2=87654321, G3=5678, G4=1234 5000 100000 10 2000
Prior Distributions	$E_0 \sim Uniform[-1000, -1]$ $E_{max} \sim Normal\ (0, SD = 1000)$ $ED_{50} \sim Uniform[0.001, 8]$ $a, b \sim Normal\ (0, SD = 1000)$ $\sigma_t \sim Inv.Gamma\ (shape = 0.001, scale = 0.001)$ $\theta_t \sim Uniform[-1, 1]$

Table 6. Monte Carlo Standard Error (MCSE) and ratio to the estimated Standard Deviation (SD) of the posterior distribution (mean value across all 1000 datasets).

	Gauss Copula Model		
	MCSE	**SD**	**MCSE/SD**
E_0	<0.01	0.12	0.01
E_{max}	<0.01	0.04	0.01
ED_{50}	0.29	14.84	0.02
a	0.02	0.77	0.03
b	0.44	23.46	0.02
σ_1	0.18	10.66	0.02
σ_2	0.17	10.56	0.02
σ_3	0.17	10.58	0.02
σ_4	0.17	10.56	0.02
σ_5	0.17	10.28	0.02
σ_6	0.17	10.11	0.02
ρ_1	<0.01	0.13	0.02
ρ_2	<0.01	0.13	0.02
ρ_3	<0.01	0.13	0.02
ρ_4	<0.01	0.13	0.02
ρ_5	<0.01	0.09	0.02
ρ_6	<0.01	0.07	0.02

6.3.   Example 3

For both copula models in Example 3, the 1000 datasets were split into 10 groups with 100 datasets in each group. The grouped datasets were then run with identical programs with different starting seeds (details below).

MCMC Characteristic	Values Used
Random Seed	G1=012345, G2=112345, G3=212345, G4=312345, G5=412345
	G6=512345, G7=612345, G8=712345, G9=812345, G10=912345
Burn in	1000
Chain Length	5000
Chain Thinning	5
Tuning Loops	2000
Prior Distributions	$\beta_{jt} \sim Normal\,(0, \text{SD} = 1000)$
	$\varphi_t, \sigma_t \sim Inv.\,Gamma\,(shape = 0.001, scale = 0.001)$
	$\omega_t^{jk} \sim Uniform[-1,1]$

Table 7. Monte Carlo Standard Error (MCSE) and ratio to the estimated Standard Deviation (SD) of the posterior distribution (mean value across all 1000 datasets).

	GCMR			ICMR		
	MCSE	SD	MCSE/SD	MCSE	SD	MCSE/SD
μ_1	0.65	10.15	0.06	0.60	10.06	0.06
μ_2	0.69	10.01	0.07	0.67	10.04	0.07
p_1	<0.01	0.03	0.07	<0.01	0.03	0.07
p_2	<0.01	0.05	0.07	<0.01	0.05	0.07
r_1	0.02	0.28	0.07	0.02	0.28	0.07
r_2	0.01	0.20	0.07	0.01	0.21	0.07
σ_1	0.33	7.35	0.04	0.31	7.23	0.04
σ_2	0.38	7.13	0.05	0.32	7.21	0.04
ω_1	0.01	0.14	0.05	0.01	0.14	0.04
ω_2	0.01	0.16	0.05	0.01	0.17	0.04
θ_1^{12}	0.01	0.16	0.07	-	-	-
θ_1^{13}	0.01	0.10	0.07	-	-	-
θ_1^{23}	0.01	0.14	0.07	-	-	-
θ_2^{12}	<0.01	0.06	0.08	-	-	-
θ_2^{13}	0.01	0.09	0.07	-	-	-
θ_2^{23}	0.00	0.06	0.08	-	-	-

6.4.   Real Data Example: Single Efficacy and Safety Endpoints

MCMC Characteristic	Values Used
Random Seed Burn in Chain Length Chain Thinning Tuning Loops Prior Distributions	123456 1000 100000 50 1000 $\beta_{jt} \sim Normal\,(0, \mathrm{SD} =\ 1000)$ $\upsilon_t, \tau_t \sim Inv.\,Gamma\,(shape =\ 0.01, scale\ =\ 0.01)$

6.5.   Real Data Example: Single Efficacy and Two Safety Endpoints

MCMC Characteristic	Values Used
Random Seed Burn in Chain Length Chain Thinning Tuning Loops Prior Distributions	987654321 5000 50000 2 2000 $\beta_{jt} \sim Normal\,(0, \mathrm{SD} =\ 1000)$ $\varphi_t, \sigma_t \sim Inv.\,Gamma\,(shape =\ 0.001, scale\ =\ 0.001)$ $\omega_t^{jk} \sim Uniform[-1,1]$

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