Supporting information for Bayesian modeling of a bivariate toxicity outcome for early phase oncology trials evaluating dose regimens by Emma Gerard, Sarah Zohar, Christelle Lorenzato, Moreno Ursino and Marie-Karelle Riviere

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Web Appendix A: Additional results

Web Appendix A.1: Example from a single simulated trial

Figure 1 shows the fit of the PD profile of patient 10 who receives dose regimen $\boldsymbol{S_3}$. For this patient, the global peak of cytokine is reached after administration 4, its estimated value is 600.26 pg/mL.

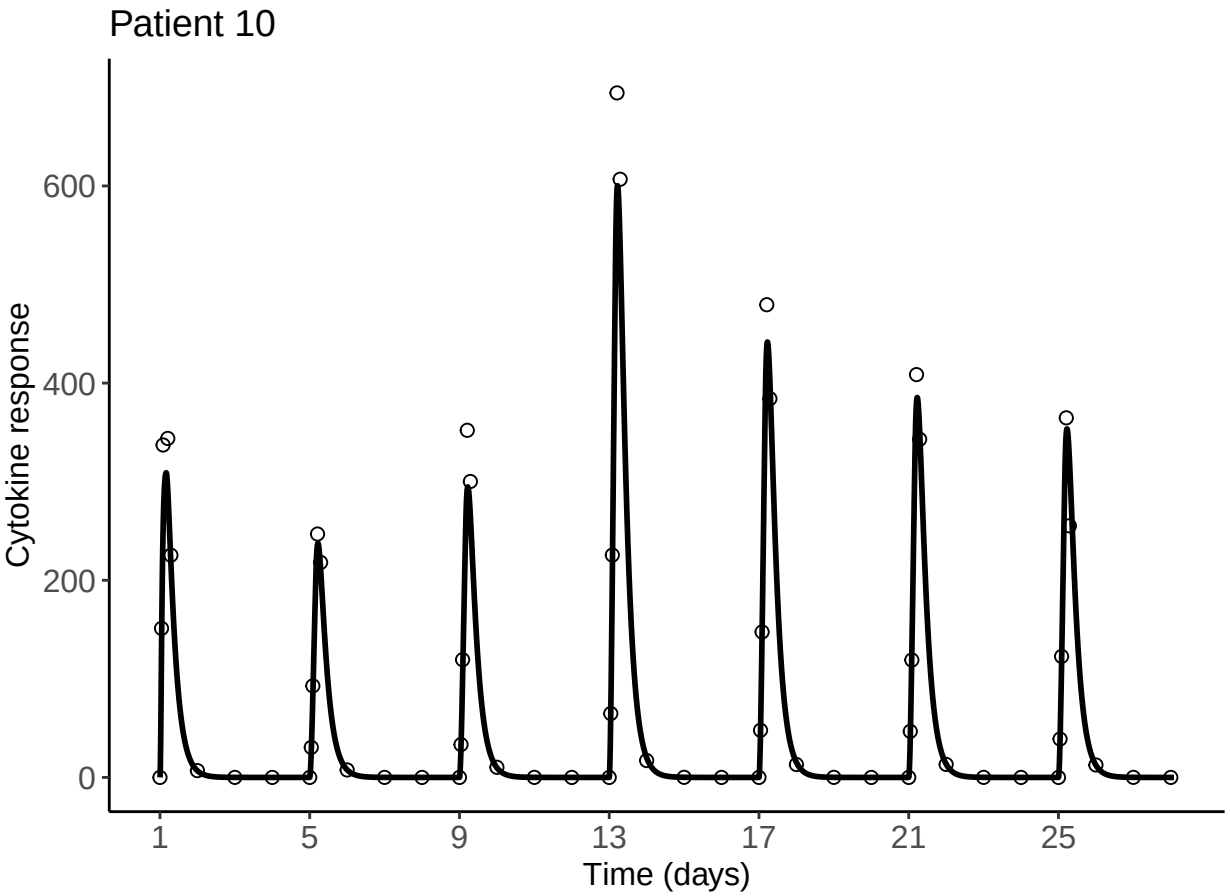

Figure 1: Estimated cytokine profile of patient 10 receiving $\boldsymbol{S_3}$ and having (Cl=1.99, V=3.95, E_{max}=645257, EC_{50}=10000, H=0.96, I_{max}=1, IC_{50}=18200, k_{deg}=0.21, K=2.43) as individual PK/PD parameters. The dots represent the sampled cytokine responses and the continuous line shows the fitted cytokine response.

The posterior distributions of the probabilities of CRS, DLT_o, DLT_o|noCRS and DLT of dose regimen $\boldsymbol{S_4}$ are represented in Figure 2.

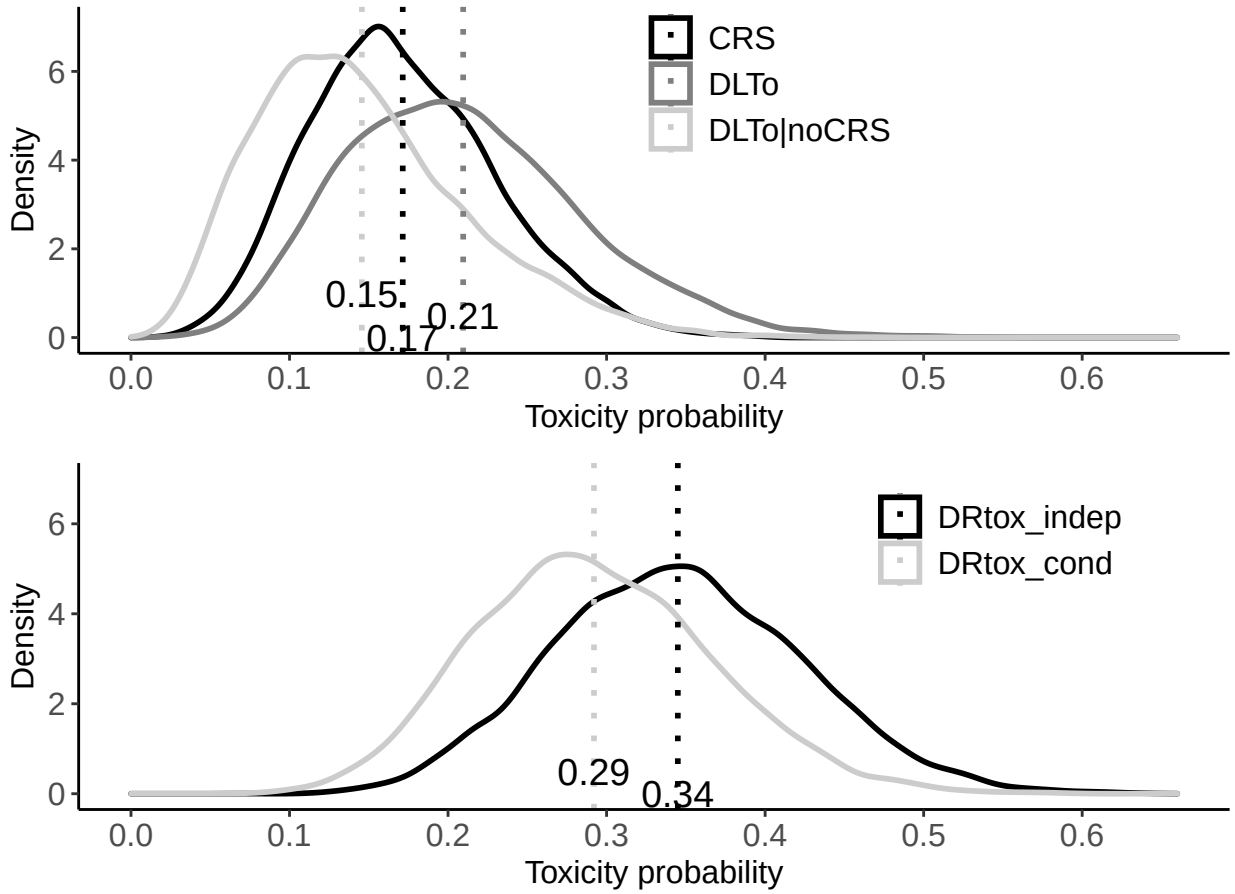

Figure 2: Estimated posterior distributions of CRS, DLT_o and DLT_o|noCRS in the upper part of the Figure, and of DLT for the DRtox_indep and DRtox_cond in the lower part, for dose regimen $\boldsymbol{S_4}$. The dotted vertical lines represent the posterior means.

Web Appendix A.2: Estimation of the toxicity curves

In the main paper, we presented the results of our proposed methods in terms of the proportion of correct selection (PCS). We illustrate here the results in terms of estimation of the different probabilities of toxicity. The estimated probabilities of DLT, CRS and DLT_o for Scenarios 2, 5 and 6 are displayed in Figures 3, 4 and 5. All three joint methods and the CRM well estimate the probability of DLT of the MTD-regimen in all scenarios. The probability of CRS of all dose regimens is well estimated by the three joint approaches via the logistic-DRtox. In Scenarios 2 and 6, both the DRtox_indep and DRtox_copula under-estimate the marginal probability of DLT_o as they estimate it to be similar to the conditional probability of DLT_o given no CRS. However, the DRtox_cond has a correct estimation of the conditional probability of DLT_o given no CRS of the MTD-regimen. The under-estimation of the marginal probability of DLT_o is due to the fact that the drug administration is stopped in case a DLT occurs (either a CRS or DLT_o) and that the CRS has a tendency to occur at the beginning of the regimens while the DLT_o occurs at the end. Therefore, when a patient experiences a CRS, s/he does not receive the remaining administrations planned of the regimen that may have caused a DLT_o. The conditional probability of DLT_o given that a CRS occurred can then only be estimated when a CRS and DLT_o occur at the same time, which is rare.

In Scenario 5, where the MTD-regimen is the last one of the set, the probability of DLT of the MTD-regimen is well estimated by the three joint approaches and the CRM, but the joint approaches over-estimate the probability of DLT of S_5, which results in a loss of PCS. Both the probabilities of CRS and DLT_o of S_5 are over-estimated as in this scenario very few DLT are observed, therefore our joint approaches have difficulty in distinguishing regimens S_5 and S_6.

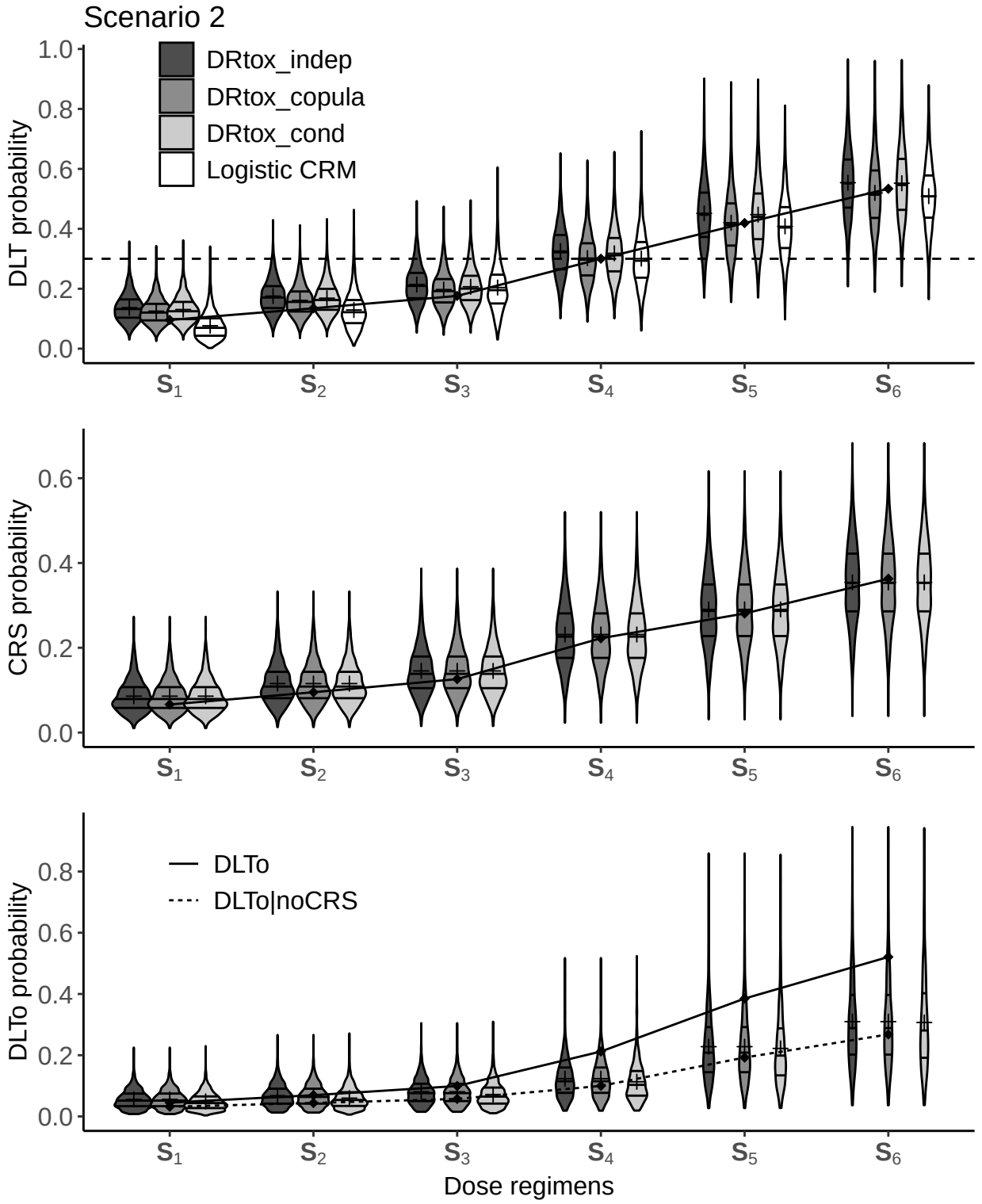

Figure 3: Violin plots of the estimated probabilities of DLT, CRS and DLT_o in Scenario 2 for 1000 simulated trials. All three joint approaches and the CRM estimate the probability of DLT in the first part of the figure, where the dashed line represents the toxicity target and the solid line represents the true DLT probabilities. Our three joint approches estimate the probability of CRS with the logistic DRtox in the second part of the figure, where the solid line represents the true CRS probabilities. In the last part of the figure, both the DRtox_indep and DRtox_copula estimate the marginal probability of DLT_o while the DRtox_cond estimates the conditional probability of DLT_o given no CRS has occurred. The solid line represents the true marginal probabilities of DLT_o while the dotted line represents the true conditional probabilities of DLT_o given no CRS. In all the figure, horizontal lines on the density estimates represent the median and first and third quantiles of the distributions, and the plus sign represents the mean.

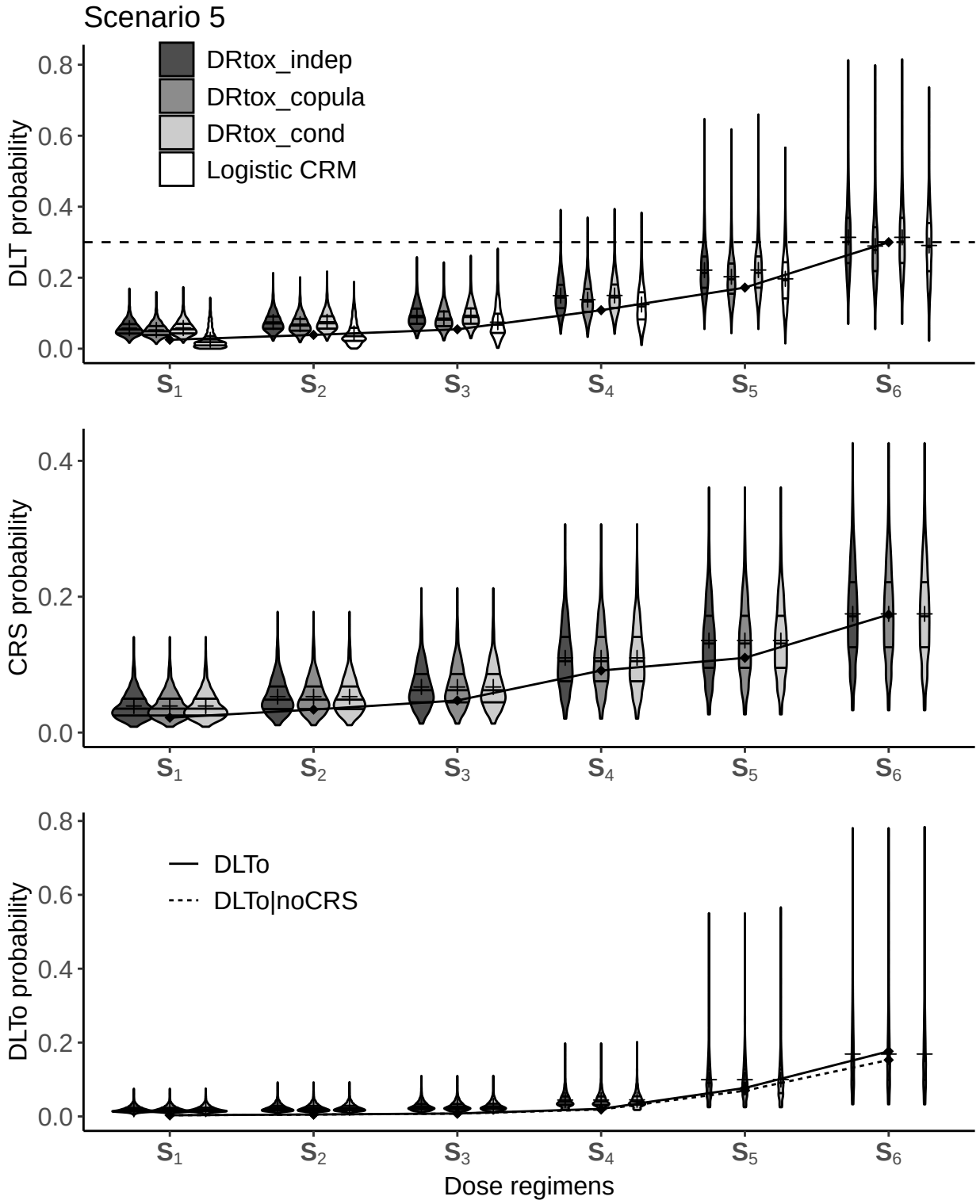

Figure 4: Violin plots of the estimated probabilities of DLT, CRS and DLT_o in Scenario 5 for 1000 simulated trials. All three joint approaches and the CRM estimate the probability of DLT in the first part of the figure, where the dashed line represents the toxicity target and the solid line represents the true DLT probabilities. Our three joint approches estimate the probability of CRS with the logistic DRtox in the second part of the figure, where the solid line represents the true CRS probabilities. In the last part of the figure, both the DRtox_indep and DRtox_copula estimate the marginal probability of DLT_o while the DRtox_cond estimates the conditional probability of DLT_o given no CRS has occurred. The solid line represents the true marginal probabilities of DLT_o while the dotted line represents the true conditional probabilities of DLT_o given no CRS. In all the figure, horizontal lines on the density estimates represent the median and first and third quantiles of the distributions, and the plus sign represents the mean.

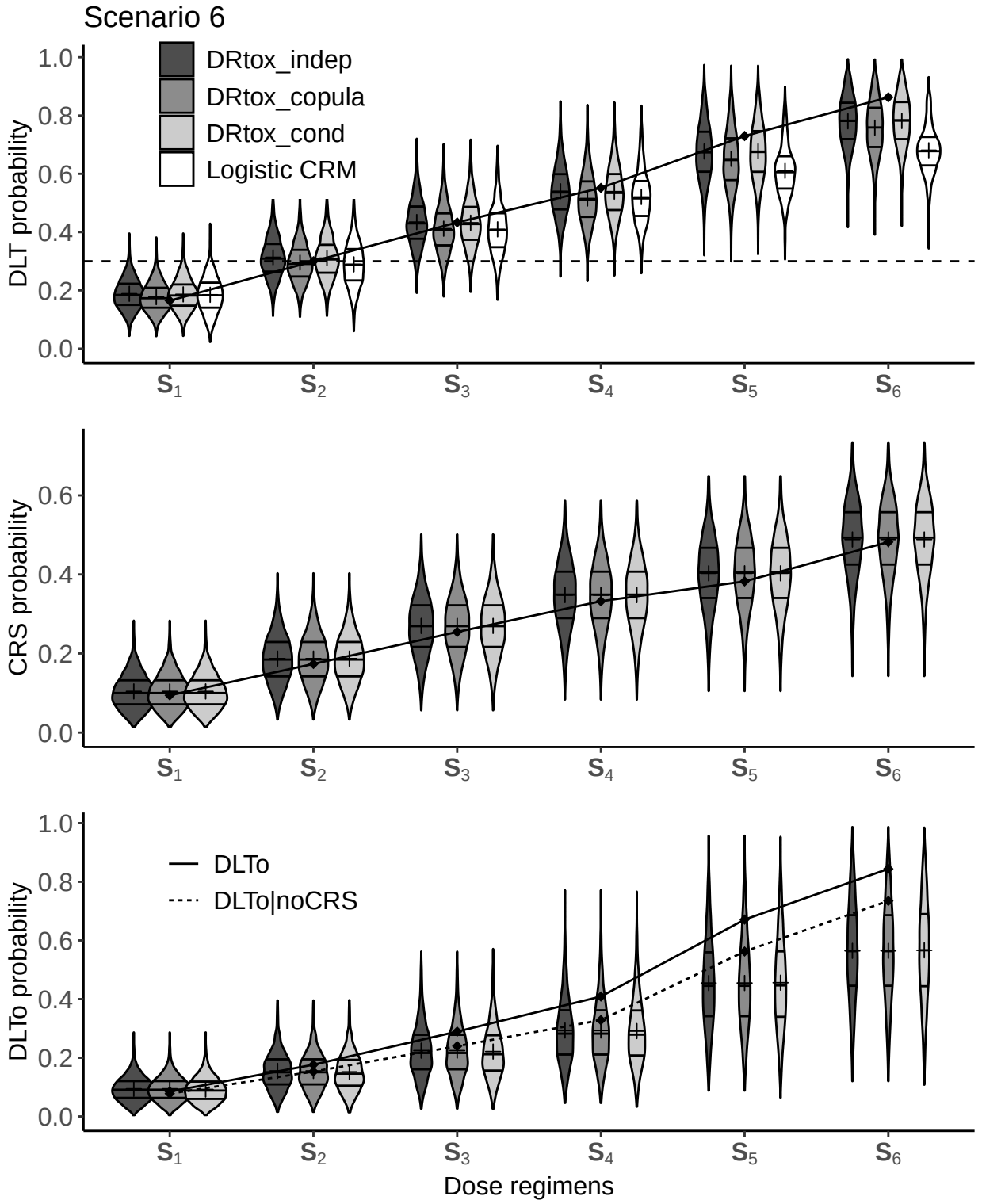

Figure 5: Violin plots of the estimated probabilities of DLT, CRS and DLT_o in Scenario 6 for 1000 simulated trials. All three joint approaches and the CRM estimate the probability of DLT in the first part of the figure, where the dashed line represents the toxicity target and the solid line represents the true DLT probabilities. Our three joint approches estimate the probability of CRS with the logistic DRtox in the second part of the figure, where the solid line represents the true CRS probabilities. In the last part of the figure, both the DRtox_indep and DRtox_copula estimate the marginal probability of DLT_o while the DRtox_cond estimates the conditional probability of DLT_o given no CRS has occurred. The solid line represents the true marginal probabilities of DLT_o while the dotted line represents the true conditional probabilities of DLT_o given no CRS. In all the figure, horizontal lines on the density estimates represent the median and first and third quantiles of the distributions, and the plus sign represents the mean.

Web Appendix A.3: Various associations between the CRS and the DLT_o

We studied the effect of varying the association between the CRS and the DLT_o, measured by the mean risk ratio (RR), and defined three additional scenarios on Set A:

- Scenario 7: moderate positive association (RR=3.31)
- Scenario 8: independence between toxicities (RR=1)
- Scenario 9: negative association (RR=0.52)

The PCS results on these additional scenarios for our three joint approaches and the CRM are displayed in Table 1. Our approaches still outperform the CRM, and the three approaches have similar results except when increasing the correlation between the CRS and the DLT_o: the DRtox_copula and DRtox_cond have higher PCS as they account for the association between toxicities. We can also note that the DRtox_copula, that assumes a positive association between toxicities, still has good results on Scenario 9 where there is a negative association between the CRS and the DLT_o.

The estimations of the DLT probabilities in case of independence (Scenario 8), small association (Scenario 1) and high association (Scenario 2) are represented in Figure 6. The estimations on the six dose regimens and the predictions on $\boldsymbol{S}_{\text{new1}}$ and $\boldsymbol{S}_{\text{new2}}$ are shown. The root-mean square error (RMSE) of the estimated probabilities on $\boldsymbol{S_3}$, $\boldsymbol{S_4}$, $\boldsymbol{S_5}$ (neighbors) and on $\boldsymbol{S_4}$, $\boldsymbol{S}_{\text{new1}}$, $\boldsymbol{S}_{\text{new2}}$ (predict) are represented in Figure 7. We can observe that all methods, DRtox_indep, DRtox_copula and DRtox_cond, have good estimations around the MTD-regimen in case of various associations between the CRS and the DLT_o.

Table 1: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in three additional toxicity scenarios with various associations between the CRS and the DLT_o. For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the 3 joint approaches (DRtox_indep, DRtox_copula and DRtox_cond) and the CRM. The proportions of correct selection (PCS) of the MTD-regimen are represented in bold.

Scenario	Set	RR	Method		$\boldsymbol{S_1}$	$\boldsymbol{S_2}$	$\boldsymbol{S_3}$	$\boldsymbol{S_4}$	$\boldsymbol{S_5}$	$\boldsymbol{S_6}$
7	A	3.31		$\boldsymbol{p_T}$	0.10	0.14	0.18	**0.30**	0.44	0.57
				$\boldsymbol{p_T^{(1)}}$	0.06	0.08	0.11	**0.19**	0.24	0.32
				$\boldsymbol{p_T^{(2)}}$	0.05	0.07	0.10	**0.19**	0.37	0.53
			DRtox_indep		0	4	25	**54**	15	3
			DRtox_copula		0	1	18	**56**	21	4
			DRtox_cond		0	3	23	**55**	17	3
			Logistic CRM		0	4	20	**46**	23	7
8	A	1.00		$\boldsymbol{p_T}$	0.10	0.14	0.18	**0.30**	0.45	0.59
				$\boldsymbol{p_T^{(1)}}$	0.04	0.07	0.09	**0.16**	0.20	0.27
				$\boldsymbol{p_T^{(2)}}$	0.06	0.08	0.10	**0.16**	0.31	0.44
			DRtox_indep		0	3	24	**57**	15	1
			DRtox_copula		0	1	16	**58**	22	2
			DRtox_cond		0	3	23	**57**	15	1
			Logistic CRM		0	3	22	**47**	23	5
9	A	0.52		$\boldsymbol{p_T}$	0.10	0.14	0.18	**0.30**	0.45	0.59
				$\boldsymbol{p_T^{(1)}}$	0.04	0.06	0.09	**0.16**	0.20	0.27
				$\boldsymbol{p_T^{(2)}}$	0.06	0.08	0.09	**0.15**	0.28	0.39
			DRtox_indep		0	3	21	**58**	16	1
			DRtox_copula		0	1	15	**58**	23	3
			DRtox_cond		0	4	22	**58**	16	1
			Logistic CRM		0	4	20	**48**	23	5

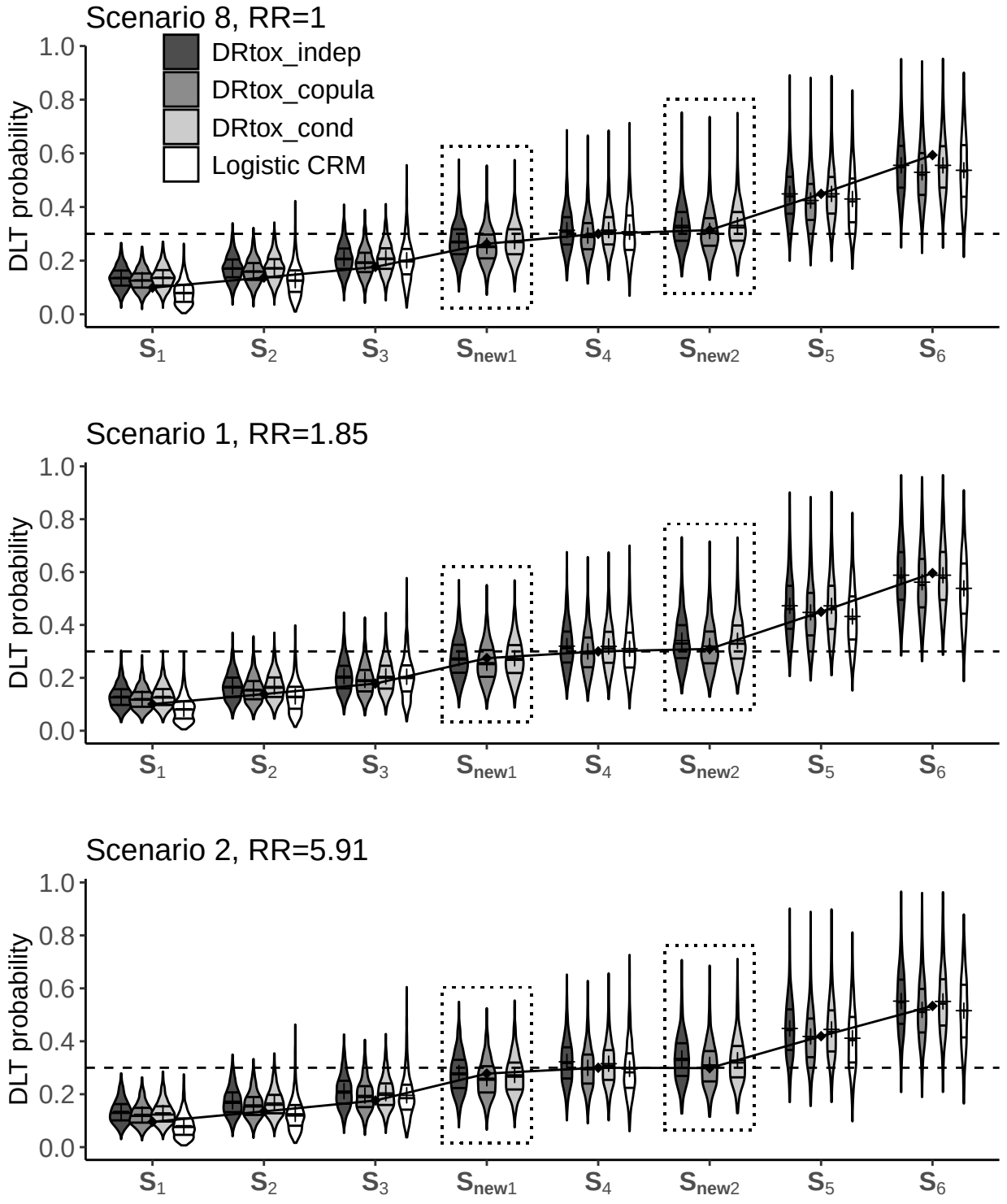

Figure 6: Violin plots of the estimated probabilities of DLT when increasing association between the CRS and DLT_o (Scenarios 8, 1 and 2) for the six dose regimens of the panel and two additional dose regimens ($\boldsymbol{S}_{\text{new1}}$ and $\boldsymbol{S}_{\text{new2}}$), on 1000 trials with the three proposed joint approaches and the CRM. The predicted DLT probabilities of the new dose regimens are framed in dotted line. Horizontal lines on the density estimates represent the median and first and third quantiles of the distributions, and the plus sign represents the mean. The dashed line represents the toxicity target, and the solid line represents the true DLT probabilities

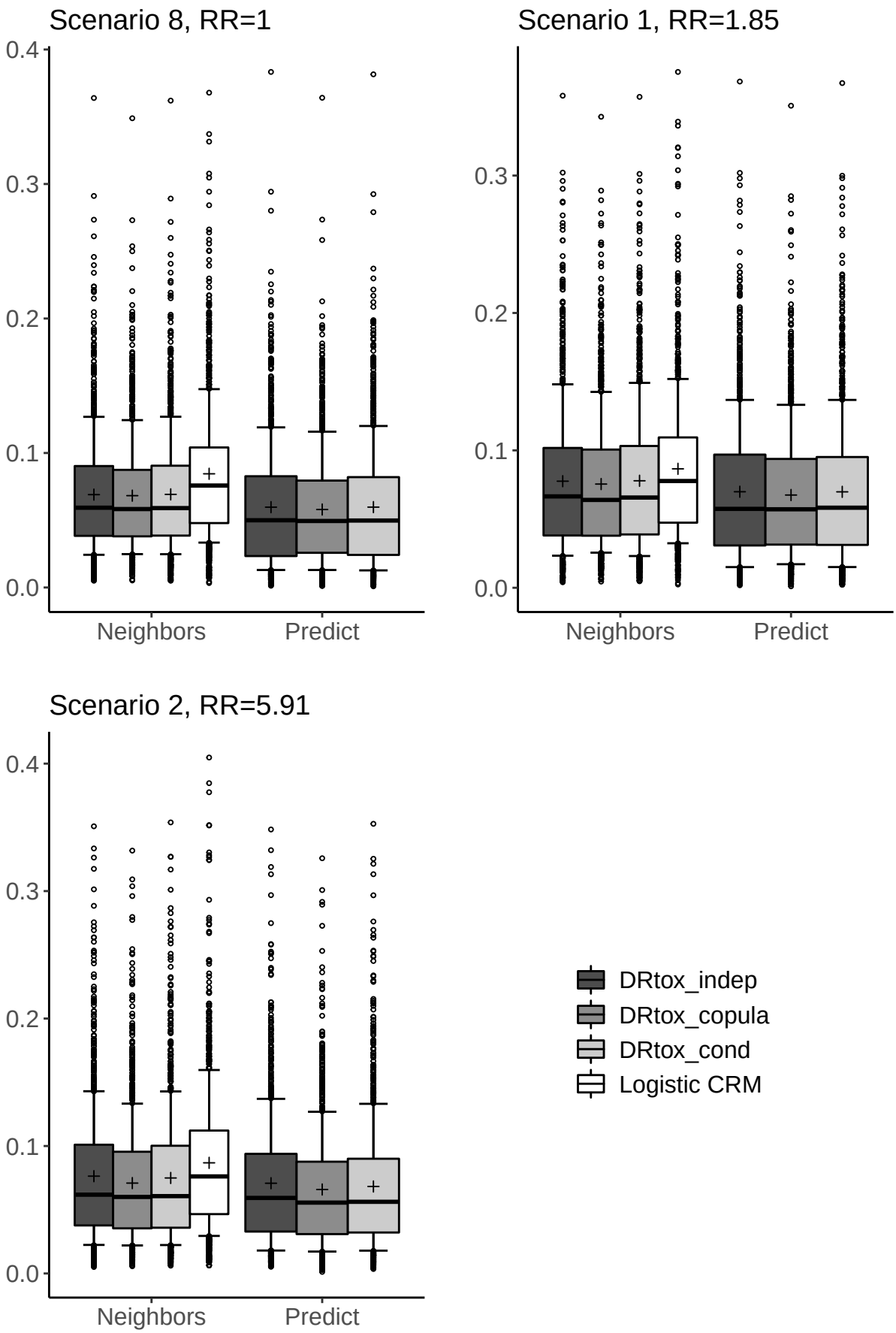

Figure 7: Boxplots of the RMSE of the estimated DLT probabilities on $\boldsymbol{S_3}$, $\boldsymbol{S_4}$, $\boldsymbol{S_5}$ (neighbors) and on $\boldsymbol{S_4}$, $\boldsymbol{S}_{\text{new1}}$, $\boldsymbol{S}_{\text{new2}}$ (predict) when increasing association between the CRS and DLT_o (Scenarios 8, 1 and 2) on 1000 trials. The plus sign represents the mean and error bars represent the first and ninth deciles.

Web Appendix A.4: Simpler model on the DLT_o

To compute the DRtox_cond approach, we modeled the DLT_o with a cumulative model using the cumulative dose to account for the dose regimen. We evaluated the effect of a simpler model on the DLT_o without taking into account the multiple administrations. We defined the conditional probability of DLT_o given that no CRS has occurred as follows:

$$p_{i\star}^{(2)} = \mathbb{P}\left(Y_i^{(2)} = 1 \middle| Y_i^{(1)} = 0\right) \tag{1}$$

We then defined the following model on the conditional probability of DLT_o that is very similar to the 2-parameter logistic model of the CRM:

$$\text{logit}\left(p_{i\star}^{(2)}\right) = a + b \ \text{logit}\left(\pi_{k_i}^{(2)}\right) \tag{2}$$

where $\pi_{k_i}^{(2)}$ is the prior guess of the DLT_o probability of dose regimen S_{k_i} that is planned for patient i. We initially assume that the probabilities of CRS and DLT_o are independent and equal, therefore $\pi_{k_i}^{(2)} = 1 - \sqrt{1 - \pi_{k_i}}$. For the prior distributions, we considered $a \sim \mathcal{N}\left(0, \sqrt{10}\right)$ and $b \sim \gamma(1, 1)$ to ensure positivity.

Let DRtox_cond_simple be the joint approach built on the conditional formulation and using the simpler model on the DLT_o defined in Equation 2. The PCS of the DRtox_cond_simple and DRtox_cond are displayed in Table 2 for the six main scenarios. The only case where the simpler model is better is in Scenario 5 where the MTD-regimen is the last one of the set and therefore few DLT_o are observed. In this case, distinguishing the different regimens becomes challenging for the cumulative model in the DRtox_cond.

Table 2: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in the six main toxicity scenarios. For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the joint approach defined from the conditional formulation using either the cumulative model (DRtox_cond) or the simpler model on the DLT_o (DRtox_cond_simple). The proportions of correct selection (PCS) of the MTD-regimen are represented in bold.

Scenario	Set	RR	Method		S_1	S_2	S_3	S_4	S_5	S_6
1	A	1.85		p_T	0.10	0.14	0.18	**0.30**	0.45	0.60
				$p_T^{(1)}$	0.05	0.07	0.10	**0.18**	0.22	0.30
				$p_T^{(2)}$	0.06	0.08	0.10	**0.17**	0.34	0.50
			DRtox_cond		0	3	25	**55**	16	2
			DRtox_cond_simple		0	4	27	**50**	16	2
2	A	5.91		p_T	0.10	0.13	0.18	**0.30**	0.42	0.53
				$p_T^{(1)}$	0.07	0.10	0.13	**0.22**	0.28	0.36
				$p_T^{(2)}$	0.04	0.07	0.10	**0.21**	0.39	0.52
			DRtox_cond		0	3	23	**52**	18	4
			DRtox_cond_simple		1	4	23	**49**	20	4
3	A	1.81		p_T	0.11	0.15	0.18	**0.30**	0.45	0.59
				$p_T^{(1)}$	0.03	0.05	0.07	**0.13**	0.16	0.23
				$p_T^{(2)}$	0.08	0.11	0.13	**0.22**	0.39	0.54
			DRtox_cond		1	3	22	**58**	15	2
			DRtox_cond_simple		1	5	27	**50**	15	2
4	A	1.90		p_T	0.09	0.13	0.17	**0.30**	0.44	0.59
				$p_T^{(1)}$	0.07	0.10	0.13	**0.23**	0.29	0.37
				$p_T^{(2)}$	0.03	0.04	0.06	**0.12**	0.27	0.43
			DRtox_cond		0	3	24	**55**	15	2
			DRtox_cond_simple		0	4	25	**52**	16	3
5	A	1.97		p_T	0.03	0.04	0.05	0.11	0.17	**0.30**
				$p_T^{(1)}$	0.02	0.03	0.05	0.09	0.11	**0.17**
				$p_T^{(2)}$	0.00	0.01	0.01	0.02	0.08	**0.18**
			DRtox_cond		0	0	0	4	29	**67**
			DRtox_cond_simple		0	0	0	4	20	**76**
6	B	1.70		p_T	0.16	**0.30**	0.43	0.55	0.73	0.86
				$p_T^{(1)}$	0.09	**0.17**	0.25	0.33	0.38	0.48
				$p_T^{(2)}$	0.08	**0.18**	0.29	0.41	0.67	0.84
			DRtox_cond		19	**65**	15	1	0	0
			DRtox_cond_simple		21	**63**	15	1	0	0

Web Appendix B: Sensitivity analysis

Web Appendix B.1: Sensitivity to prior effective sample size

We evaluated the effect of varying the amount of information provided by the prior distributions that we measured by approximating the effective sample size (ESS). We studied three different ESS to evaluate the effect of almost no prior information (ESS=0.2), medium prior information (ESS=2) and strong prior information (ESS=7).

The case of almost no prior information, ESS=0.2, was obtained with $\sigma_{\beta_{0,1}} = 10$ $\alpha = 5$ for the CRS model and $\sigma_{\beta_{0,2}} = 10$ and $\sigma_{\beta_{1,2}} = 1$ for the DLT_o model. The case of medium prior association, ESS=2, was obtained with $\sigma_{\beta_{0,1}} = 2$ $\alpha = 5$ for the CRS model and $\sigma_{\beta_{0,2}} = 2$ and $\sigma_{\beta_{1,2}} = 1$ for the DLT_o model. The case of strong prior information, ESS=7, was obtained with $\sigma_{\beta_{0,1}} = 1$ $\alpha = 5$ for the CRS model and $\sigma_{\beta_{0,2}} = 1$ and $\sigma_{\beta_{1,2}} = 0.45$ for the DLT_o model.

PCS with these increasing ESS for the DRtox_indep, DRtox_copula and DRtox_cond can be found in Table 3 for Scenarios 1, 2 and 3 and in Table 4 for Scenarios 4, 5 and 6. Increasing the prior ESS leads to better results when the prior guesses of DLT probabilities are close to the truth (Scenarios 1-4 where $\boldsymbol{S_4}$ is the true MTD-regimen), but also when the initial guesses of DLT probabilities underestimate the true DLT probabilities (Scenario 6 where $\boldsymbol{S_2}$ is the true MTD-regimen). However, increasing the prior ESS leads to poorer results when the initial guesses of DLT probabilities overestimate the true DLT probabilities (Scenario 5 where $\boldsymbol{S_6}$ is the true MTD-regimen).

Table 3: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in Scenarios 1, 2 and 3 for increasing ESS. For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the 3 joint approaches (DRtox_indep, DRtox_copula and DRtox_cond) and the CRM. The proportions of correct selection (PCS) of the MTD-regimen are represented in bold.

Scenario	Set	RR	Method	ESS		S_1	S_2	S_3	S_4	S_5	S_6
					p_T	0.10	0.14	0.18	**0.30**	0.45	0.60
					$p_T^{(1)}$	0.05	0.07	0.10	**0.18**	0.22	0.30
					$p_T^{(2)}$	0.06	0.08	0.10	**0.17**	0.34	0.50
			DRtox_indep	0.2		0	3	22	**53**	18	2
				2		0	4	24	**55**	15	2
1	A	1.85		7		0	3	30	**57**	9	0
			DRtox_copula	0.2		0	2	19	**51**	24	4
				2		0	2	20	**55**	20	3
				7		0	1	21	**61**	16	1
			DRtox_cond	0.2		0	3	22	**52**	19	3
				2		0	3	25	**55**	15	2
				7		0	3	31	**57**	9	0
					p_T	0.10	0.13	0.18	**0.30**	0.42	0.53
					$p_T^{(1)}$	0.07	0.10	0.13	**0.22**	0.28	0.36
					$p_T^{(2)}$	0.04	0.07	0.10	**0.21**	0.39	0.52
			DRtox_indep	0.2		1	4	23	**46**	20	6
				2		0	4	27	**48**	16	3
2	A	5.91		7		0	5	31	**54**	9	1
			DRtox_copula	0.2		0	3	15	**50**	24	8
				2		0	3	17	**52**	24	5
				7		0	2	20	**60**	15	3
			DRtox_cond	0.2		1	3	20	**49**	22	6
				2		0	3	24	**52**	18	4
				7		0	3	30	**56**	9	1
					p_T	0.11	0.15	0.18	**0.30**	0.45	0.59
					$p_T^{(1)}$	0.03	0.05	0.07	**0.13**	0.16	0.23
					$p_T^{(2)}$	0.08	0.11	0.13	**0.22**	0.39	0.54
			DRtox_indep	0.2		1	4	20	**55**	18	2
				2		1	3	22	**58**	15	2
3	A	1.81		7		1	2	26	**62**	8	0
			DRtox_copula	0.2		1	2	15	**53**	24	4
				2		1	2	16	**59**	20	2
				7		0	1	16	**64**	18	1
			DRtox_cond	0.2		1	3	19	**56**	19	2
				2		1	3	21	**58**	16	2
				7		1	2	26	**62**	9	0

Table 4: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in Scenarios 4, 5 and 6 for increasing ESS. For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the 3 joint approaches (DRtox_indep, DRtox_copula and DRtox_cond) and the CRM. The proportions of correct selection (PCS) of the MTD-regimen are represented in bold.

Scenario	Set	RR	Method	ESS		S_1	S_2	S_3	S_4	S_5	S_6
					p_T	0.09	0.13	0.17	**0.30**	0.44	0.59
					$p_T^{(1)}$	0.07	0.10	0.13	**0.23**	0.29	0.37
					$p_T^{(2)}$	0.03	0.04	0.06	**0.12**	0.27	0.43
			DRtox_indep	0.2		1	3	22	**52**	19	4
				2		0	3	24	**56**	14	2
4	A	1.90		7		0	3	29	**59**	8	0
			DRtox_copula	0.2		0	2	17	**52**	24	5
				2		0	2	19	**56**	20	4
				7		0	2	21	**61**	14	2
			DRtox_cond	0.2		1	3	21	**53**	18	4
				2		0	3	24	**55**	14	2
				7		0	3	31	**57**	8	0
					p_T	0.03	0.04	0.05	0.11	0.17	**0.30**
					$p_T^{(1)}$	0.02	0.03	0.05	0.09	0.11	**0.17**
					$p_T^{(2)}$	0.00	0.01	0.01	0.02	0.08	**0.18**
			DRtox_indep	0.2		0	0	0	3	20	**78**
				2		0	0	0	4	29	**67**
5	A	1.97		7		0	0	0	10	43	**47**
			DRtox_copula	0.2		0	0	0	2	15	**83**
				2		0	0	0	3	20	**77**
				7		0	0	0	5	32	**63**
			DRtox_cond	0.2		0	0	0	3	19	**78**
				2		0	0	0	4	29	**67**
				7		0	0	0	10	43	**47**
					p_T	0.16	**0.30**	0.43	0.55	0.73	0.86
					$p_T^{(1)}$	0.09	**0.17**	0.25	0.33	0.38	0.48
					$p_T^{(2)}$	0.08	**0.18**	0.29	0.41	0.67	0.84
			DRtox_indep	0.2		24	**60**	14	1	0	0
				2		20	**64**	15	1	0	0
6	B	1.70		7		13	**72**	15	0	0	0
			DRtox_copula	0.2		18	**60**	20	2	0	0
				2		14	**62**	21	2	0	0
				7		6	**68**	25	1	0	0
			DRtox_cond	0.2		22	**61**	15	1	0	0
				2		19	**65**	16	1	0	0
				7		12	**71**	16	0	0	0

Web Appendix B.2: Sensitivity to prior distribution

To evaluate the effect of the prior distribution on the DRtox_cond, we compared the results when using a gamma distribution on the slope or a normal distribution on the logarithm of the slope for both the CRS model and the DLT_o model.

For the CRS model, we considered:

- Gamma prior: $\text{logit}\left(\mathbb{P}\left(Y_i^{(1)}=1\right)\right)=\beta_{0,1}+\beta_{1,1}\log\left(\frac{r_i^M}{\overline{r}_{k_T}^M}\right)$, where $\beta_{1,1}\sim\gamma\left(\alpha_1,\frac{\alpha_1}{\overline{\beta}_{1,1}}\right)$
- Normal prior: $\text{logit}\left(\mathbb{P}\left(Y_i^{(1)}=1\right)\right)=\beta_{0,1}+\exp\left(\beta_{1,1}\right)\log\left(\frac{r_i^M}{\overline{r}_{k_T}^M}\right)$, where $\beta_{1,1}\sim\mathcal{N}\left(\overline{\beta}_{1,1},\sigma^2_{\beta_1}\right)$

For the DLT_o model, we consider:

- Gamma prior: $\text{logit}\left(p_{i,j\star}^{(2)^{\text{cum}}}\right)=\beta_{0,2\star}+\beta_{1,2\star}\log\left(\frac{\sum_{l=1}^{j}d_{i,l}}{D_{k_T}}\right)$, where $\beta_{1,2\star}\sim\gamma\left(\alpha_1,\frac{\alpha_1}{\overline{\beta}_{1,2\star}}\right)$
- Normal prior: $\text{logit}\left(p_{i,j\star}^{(2)^{\text{cum}}}\right)=\beta_{0,2\star}+\exp\left(\beta_{1,2\star}\right)\log\left(\frac{\sum_{l=1}^{j}d_{i,l}}{D_{k_T}}\right)$, where $\beta_{1,2\star}\sim\mathcal{N}\left(\overline{\beta}_{1,2\star},\sigma^2_{\beta_1}\right)$

For both the CRS and DLT_o models, we considered $\alpha_1=5$, $\sigma_{\beta_1}=1$. For the intercept, we considered $\beta_{0,1}\sim\mathcal{N}\left(\overline{\beta}_{0,1},\sigma^2_{\beta_0}\right)$ and $\beta_{0,2\star}\sim\mathcal{N}\left(\overline{\beta}_{0,2\star},\sigma^2_{\beta_0}\right)$, where $\sigma_{\beta_0}=2$.

PCS results with these various prior distributions can be found in Table 5 for the DRtox_cond approach on Scenarios 1-6. The prior distribution has little impact on the results for almost all scenarios. In Scenario 5, where the true MTD-regimen is the last dose regimen of the panel and therefore only few DLT are observed, choosing a gamma prior for the DLT_o model can lead to better results.

Table 5: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in the six main toxicity scenarios for various prior distributions (gamma or lognormal). For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the DRtox_cond. The proportions of correct selection (PCS) at the MTD-regimen are represented in bold.

Scenario	Set	RR	Method	CRS	DLT_o		S_1	S_2	S_3	S_4	S_5	S_6
1	A	1.85				p_T	0.10	0.14	0.18	**0.30**	0.45	0.60
						$p_T^{(1)}$	0.05	0.07	0.10	**0.18**	0.22	0.30
						$p_T^{(2)}$	0.06	0.08	0.10	**0.17**	0.34	0.50
			DRtox_cond	γ	γ		0	3	23	**53**	18	2
				γ	$\mathcal{N}$		0	3	25	**55**	15	2
				$\mathcal{N}$	γ		0	3	27	**54**	14	1
				$\mathcal{N}$	$\mathcal{N}$		0	3	28	**55**	12	1
2	A	5.91				p_T	0.10	0.13	0.18	**0.30**	0.42	0.53
						$p_T^{(1)}$	0.07	0.10	0.13	**0.22**	0.28	0.36
						$p_T^{(2)}$	0.04	0.07	0.10	**0.21**	0.39	0.52
			DRtox_cond	γ	γ		0	3	22	**51**	20	4
				γ	$\mathcal{N}$		0	3	24	**52**	18	4
				$\mathcal{N}$	γ		0	4	26	**54**	14	2
				$\mathcal{N}$	$\mathcal{N}$		0	4	27	**54**	13	2
3	A	1.81				p_T	0.11	0.15	0.18	**0.30**	0.45	0.59
						$p_T^{(1)}$	0.03	0.05	0.07	**0.13**	0.16	0.23
						$p_T^{(2)}$	0.08	0.11	0.13	**0.22**	0.39	0.54
			DRtox_cond	γ	γ		1	2	19	**57**	18	2
				γ	$\mathcal{N}$		1	3	21	**58**	16	2
				$\mathcal{N}$	γ		1	3	22	**57**	16	1
				$\mathcal{N}$	$\mathcal{N}$		1	3	23	**59**	13	1
4	A	1.90				p_T	0.09	0.13	0.17	**0.30**	0.44	0.59
						$p_T^{(1)}$	0.07	0.10	0.13	**0.23**	0.29	0.37
						$p_T^{(2)}$	0.03	0.04	0.06	**0.12**	0.27	0.43
			DRtox_cond	γ	γ		1	3	24	**53**	17	3
				γ	$\mathcal{N}$		0	3	24	**55**	14	2
				$\mathcal{N}$	γ		0	4	26	**56**	12	2
				$\mathcal{N}$	$\mathcal{N}$		0	4	27	**57**	11	1
5	A	1.97				p_T	0.03	0.04	0.05	0.11	0.17	**0.30**
						$p_T^{(1)}$	0.02	0.03	0.05	0.09	0.11	**0.17**
						$p_T^{(2)}$	0.00	0.01	0.01	0.02	0.08	**0.18**
			DRtox_cond	γ	γ		0	0	0	4	21	**75**
				γ	$\mathcal{N}$		0	0	0	4	29	**67**
				$\mathcal{N}$	γ		0	0	0	4	25	**70**
				$\mathcal{N}$	$\mathcal{N}$		0	0	0	5	31	**64**
6	B	1.70				p_T	0.16	**0.30**	0.43	0.55	0.73	0.86
						$p_T^{(1)}$	0.09	**0.17**	0.25	0.33	0.38	0.48
						$p_T^{(2)}$	0.08	**0.18**	0.29	0.41	0.67	0.84
			DRtox_cond	γ	γ		19	**64**	16	1	0	0
				γ	$\mathcal{N}$		19	**65**	16	1	0	0
				$\mathcal{N}$	γ		19	**66**	15	1	0	0
				$\mathcal{N}$	$\mathcal{N}$		18	**66**	15	0	0	0

Web Appendix B.3: Sensitivity to the copula distribution

For the joint modeling approach based on a copula distribution, we evaluated two copula distributions defined as follows:

- The Clayton distribution:

$$C_\alpha\left(p_k^{(1)}, p_k^{(2)}\right) = \left(\max\left(p_k^{(1)^{-\gamma}} + p_k^{(2)^{-\gamma}} - 1, 0\right)\right)^{-1/\gamma} \tag{3}$$

where $\gamma > 0$ for positive association and $\gamma \in [-1, 0[$ for negative association.

- The Farlie–Gumbel–Morgenstern distribution:

$$C_\alpha\left(p_k^{(1)}, p_k^{(2)}\right) = p_k^{(1)} p_k^{(2)} + p_k^{(1)}\left(1 - p_k^{(1)}\right) p_k^{(2)}\left(1 - p_k^{(2)}\right) \frac{\exp(\psi) - 1}{\exp(\psi) + 1} \tag{4}$$

where $\psi = 0$ for independence, $\psi > 0$ for positive association, $\psi < 0$ for negative association.

We also evaluated various prior information on each distribution and defined 4 final joint modeling approaches based on the copula distribution as follows:

- DRtox_Clayton1: $\gamma \sim \gamma(0.1, 0.1)$
- DRtox_Clayton2: $\gamma \sim \gamma(1, 1)$ (defined as DRtox_copula in the main paper)
- DRtox_Gumbel1: $\psi \sim \mathcal{N}^+\left(0, 3^2\right)$
- DRtox_Gumbel2: $\psi \sim \mathcal{N}^+(0, 1)$

The PCS of these four variants compared to the DRtox_indep are displayed in Table 6. All 4 copula approaches have similar PCS, but the DRtox_Clayton1 and DRtox_Gumbel2 have results very close to the DRtox_indep.

The histogram of the estimated parameter of the Clayton copula for Scenarios 8, 1, 2 and the histogram of the estimated parameter of the Clayton copula for the two distributions are represented in Figure 8. We can observe on the upper part of the figure that increasing the association between toxicities has little impact on the estimation of the Clayton parameter. The lower part of the figure represents the estimation of the Clayton parameter when both toxicities are highly associated in Scenario 2 for two prior distributions. We can observe that the estimation of the parameter is highly impacted by the prior distribution chosen, even when both toxicities are strongly associated. The difficulty in estimating the copula parameter can be explained by the fact that the CRS and DLT_o rarely occur at the same time as the CRS has a tendency to occur at the beginning of the regimen while the DLT_o occurs at the end.

Table 6: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in the six main toxicity scenarios. For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the DRtox_indep and the four variants of the DRtox_copula. The proportions of correct selection (PCS) of the MTD-regimen are represented in bold.

Scenario	Set	RR	Method		S_1	S_2	S_3	S_4	S_5	S_6
				p_T	0.10	0.14	0.18	**0.30**	0.45	0.60
				$p_T^{(1)}$	0.05	0.07	0.10	**0.18**	0.22	0.30
				$p_T^{(2)}$	0.06	0.08	0.10	**0.17**	0.34	0.50
1	A	1.85	DRtox_indep		0	4	24	**55**	16	2
			DRtox_Clayton1		0	3	24	**55**	17	2
			DRtox_Clayton2		0	2	20	**55**	20	3
			DRtox_Gumbel1		0	4	25	**55**	15	2
			DRtox_Gumbel2		0	3	26	**55**	14	1
				p_T	0.10	0.13	0.18	**0.30**	0.42	0.53
				$p_T^{(1)}$	0.07	0.10	0.13	**0.22**	0.28	0.36
				$p_T^{(2)}$	0.04	0.07	0.10	**0.21**	0.39	0.52
2	A	5.91	DRtox_indep		0	4	27	**48**	16	3
			DRtox_Clayton1		0	4	23	**50**	18	4
			DRtox_Clayton2		0	3	17	**52**	24	5
			DRtox_Gumbel1		0	4	28	**48**	16	3
			DRtox_Gumbel2		0	4	28	**49**	15	4
				p_T	0.11	0.15	0.18	**0.30**	0.45	0.59
				$p_T^{(1)}$	0.03	0.05	0.07	**0.13**	0.16	0.23
				$p_T^{(2)}$	0.08	0.11	0.13	**0.22**	0.39	0.54
3	A	1.81	DRtox_indep		1	3	22	**57**	15	2
			DRtox_Clayton1		1	3	21	**57**	17	2
			DRtox_Clayton2		1	2	16	**58**	20	2
			DRtox_Gumbel1		1	3	22	**58**	14	2
			DRtox_Gumbel2		1	4	23	**57**	14	1
				p_T	0.09	0.13	0.17	**0.30**	0.44	0.59
				$p_T^{(1)}$	0.07	0.10	0.13	**0.23**	0.29	0.37
				$p_T^{(2)}$	0.03	0.04	0.06	**0.12**	0.27	0.43
4	A	1.90	DRtox_indep		0	3	24	**56**	14	2
			DRtox_Clayton1		0	3	22	**56**	15	3
			DRtox_Clayton2		0	2	19	**56**	20	4
			DRtox_Gumbel1		0	3	25	**55**	14	2
			DRtox_Gumbel2		0	3	25	**55**	14	2
				p_T	0.03	0.04	0.05	0.11	0.17	**0.30**
				$p_T^{(1)}$	0.02	0.03	0.05	0.09	0.11	**0.17**
				$p_T^{(2)}$	0.00	0.01	0.01	0.02	0.08	**0.18**
5	A	1.97	DRtox_indep		0	0	0	4	29	**67**
			DRtox_Clayton1		0	0	0	4	27	**69**
			DRtox_Clayton2		0	0	0	3	20	**77**
			DRtox_Gumbel1		0	0	0	4	29	**67**
			DRtox_Gumbel2		0	0	0	5	30	**66**
				p_T	0.16	**0.30**	0.43	0.55	0.73	0.86
				$p_T^{(1)}$	0.09	**0.17**	0.25	0.33	0.38	0.48
				$p_T^{(2)}$	0.08	**0.18**	0.29	0.41	0.67	0.84
6	B	1.70	DRtox_indep		20	**64**	15	1	0	0
			DRtox_Clayton1		19	**64**	16	1	0	0
			DRtox_Clayton2		14	**63**	21	2	0	0
			DRtox_Gumbel1		21	**64**	14	1	0	0
			DRtox_Gumbel2		22	**64**	14	0	0	0

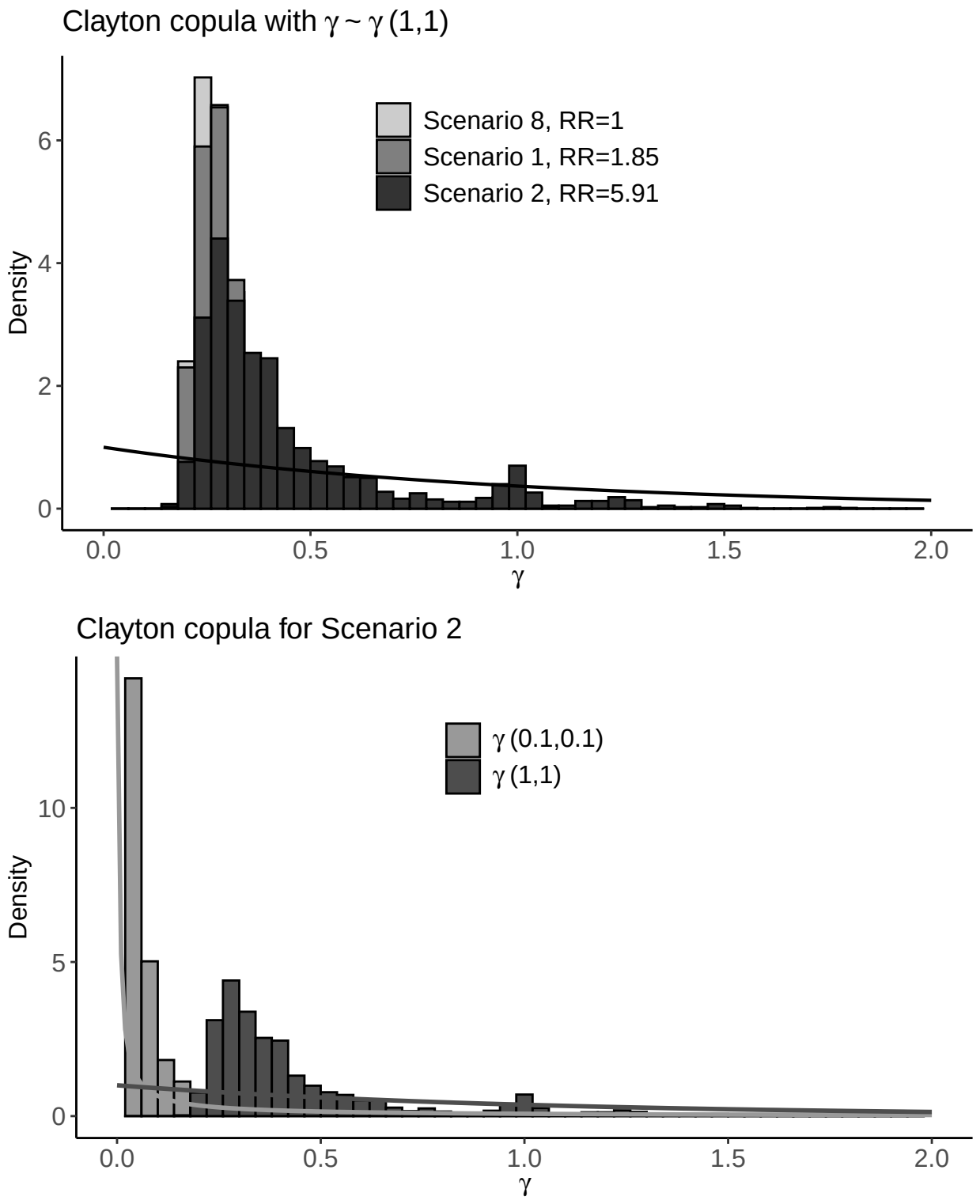

Figure 8: The upper part of the figure represents the histogram of the estimated of the Clayton distribution using $\gamma(1,1)$ for the prior distribution (named as DRtox_Clayton2) for Scenarios 8, 1 and 2. The prior distribution is represented in solid line. The lower part of the figure represents the histogram of the estimated parameter of the Clayton distribution in Scenario 2 (with a mean RR of 5.91) for the two prior distributions. Each prior distribution is represented in solid line.

Web Appendix B.4: Sensitivity to the dose escalation design

We evaluated the results obtained when the trials were simulated under an empiric CRM. The probability of DLT at dose regimen $\boldsymbol{S_k}$ is defined as $p_k = \pi_k^{\exp(\beta)}$, where π_k is the initial guess of DLT probability (skeleton) and $\beta \sim \mathcal{N}(0, 1.34)$. The skeleton is the same than the one of the logistic CRM, that is (0.06,0.12,0.20,0.30,0.40,0.50).

The PCS of our proposed methods applied at the end of the empiric CRM can be found in Table 7. In all scenarios, except Scenario 5, the PCS of our proposed methods are higher that the one of the empiric CRM. In Scenario 2, the performance of the empiric CRM is similar to the DRtox_indep. The empiric CRM gives better PCS than the logistic CRM in Scenarios 1, 2 and 4, but the impact on the performance of our proposed methods is limited. In Scenario 3 and 5, the empiric and logistic CRM have the same PCS, but the performance of our proposed methods are higher after the logistic CRM in Scenario 3 and higher after the empiric CRM in Scenario 5. In Scenario 6, the logistic CRM has better PCS than the empiric CRM, with higher performance of our proposed methods.

Table 7: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in the six main toxicity scenarios after an empiric CRM. For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the 3 joint approaches (DRtox_indep, DRtox_copula and DRtox_cond) and the empiric CRM. The proportions of correct selection (PCS) of the MTD-regimen are represented in bold.

Scenario	Set	RR	Method		S_1	S_2	S_3	S_4	S_5	S_6
1	A	1.85		p_T	0.10	0.14	0.18	**0.30**	0.45	0.60
				$p_T^{(1)}$	0.05	0.07	0.10	**0.18**	0.22	0.30
				$p_T^{(2)}$	0.06	0.08	0.10	**0.17**	0.34	0.50
			DRtox_indep		0	3	24	**55**	17	2
			DRtox_copula		0	2	18	**55**	22	3
			DRtox_cond		1	2	23	**55**	17	2
			Empiric crm		0	4	23	**50**	20	2
2	A	5.91		p_T	0.10	0.13	0.18	**0.30**	0.42	0.53
				$p_T^{(1)}$	0.07	0.10	0.13	**0.22**	0.28	0.36
				$p_T^{(2)}$	0.04	0.07	0.10	**0.21**	0.39	0.52
			DRtox_indep		0	4	28	**50**	14	3
			DRtox_copula		0	2	20	**54**	19	5
			DRtox_cond		0	4	24	**52**	16	3
			Empiric crm		0	5	22	**49**	20	4
3	A	1.81		p_T	0.11	0.15	0.18	**0.30**	0.45	0.59
				$p_T^{(1)}$	0.03	0.05	0.07	**0.13**	0.16	0.23
				$p_T^{(2)}$	0.08	0.11	0.13	**0.22**	0.39	0.54
			DRtox_indep		1	3	25	**51**	17	2
			DRtox_copula		0	2	18	**54**	22	4
			DRtox_cond		1	2	26	**52**	18	2
			Empiric crm		1	5	27	**48**	18	2
4	A	1.90		p_T	0.09	0.13	0.17	**0.30**	0.44	0.59
				$p_T^{(1)}$	0.07	0.10	0.13	**0.23**	0.29	0.37
				$p_T^{(2)}$	0.03	0.04	0.06	**0.12**	0.27	0.43
			DRtox_indep		0	3	25	**55**	15	1
			DRtox_copula		0	2	19	**57**	19	3
			DRtox_cond		0	4	24	**56**	15	1
			Empiric crm		0	4	23	**51**	20	2
5	A	1.97		p_T	0.03	0.04	0.05	0.11	0.17	**0.03**
				$p_T^{(1)}$	0.02	0.03	0.05	0.09	0.11	**0.17**
				$p_T^{(2)}$	0.00	0.01	0.01	0.02	0.08	**0.18**
			DRtox_indep		0	0	0	3	26	**71**
			DRtox_copula		0	0	0	2	16	**82**
			DRtox_cond		0	0	0	3	26	**71**
			Empiric crm		0	0	0	2	20	**77**
6	B	1.70		p_T	0.16	**0.30**	0.43	0.55	0.73	0.86
				$p_T^{(1)}$	0.09	**0.17**	0.25	0.33	0.38	0.48
				$p_T^{(2)}$	0.08	**0.18**	0.29	0.41	0.67	0.84
			DRtox_indep		22	**61**	16	0	0	0
			DRtox_copula		14	**62**	23	2	0	0
			DRtox_cond		21	**60**	17	1	0	0
			Empiric crm		18	**54**	26	2	0	0

Web Appendix C: Alternative set of dose regimens

In the main six toxicity scenarios, built either on Set A or B of the dose regimens that were inspired by the motivating trial, the CRS and DLT_o rarely occur at the same time. We then defined another set of dose regimens, Set C shown in Table 8, to increase the occurrence of both toxicities at the same time. In Set C, dose-escalation is slower than in Set A and B because the higher the steady-state dose is, the slower it is reached. We defined six additional toxicity scenarios on this new set that are similar to the main scenarios.

In Scenario 10 (similar to Scenario 1), the true MTD-regimen was S_4 that had a similar probability of CRS and DLT_o. The CRS and DLT_o were positively correlated with a average risk ratio of 1.89. In Scenario 11 (similar to Scenario 2), the association between the CRS and the DLT_o was increased to an average risk ratio of 6.37. In Scenarios 12 and 13 (similar to Scenarios 3 and 4), the true MTD-regimen remained S_4 but the proportion of each type of toxicity varied with a higher probability of DLT_o and CRS in Scenaris 12 and 13, respectively. Finally, the MTD-regimen changed to dose regimens S_6 and S_2 for Scenarios 14 and 15 (similar to Scenarios 5 and 6), respectively. The distribution of DLT, CRS and DLT_o per administration is illustrated in Figure 9 to compare the main scenarios built on Set A and B with the new scenarios built on Set C. For Scenarios 1, 5 and 6, most CRS occur at t_1 and t_4 while almost all DLT_o occur from t_4 as illustrated on the left part of the figure. However, for Scenarios 10, 14 and 15, both toxicities are more balanced throughout the drug administrations as illustrated on the right part on the figure even if CRS still tend to occur at the beginning while DLT_o occur at the end.

The proportion of selection of each dose regimen in these six new scenarios is shown in Table 9. In Scenarios 10, 11, 12 and 13, the PCS of the three joint approaches are similar to that of the CRM. All three joint approaches have a higher proportion of trials that recommend the under-dosing regimen, S_3, as the MTD-regimen. In Scenario 14, the CRM has higher PCS that the joint approaches but it was already observed in the main scenarios. Finally, on Scenario 15, where the true MTD-regimen is S_2, the three joint approaches outperform the CRM.

We represented in Figure 10 the estimated probabilities of DLT, CRS and DLT_o for the three joint approaches and the CRM for Scenario 10. We can observe that the marginal probability of CRS is slightly overestimated by the DRtox, while the probability of DLT_o (either the marginal probability of the conditional probability given no CRS) is estimated with a high variance for each joint approach. As a result, the probability of DLT at the MTD-regimen (S_4) and at the previous regimen (S_3) is also slightly overestimated by the joint approaches, which explains the higher proportion of trials that recommend S_3 as the MTD-regimen. In conclusion, in this new set of dose regimens, our joint modeling approaches do not improve the PCS compared to the CRM but they can still able to evaluate the probability of toxicity of new regimens, as illustrated in the main paper.

Table 8: Set A and Set C dose regimens used in the simulation study (in μg/kg).

		t_1	t_2	t_3	t_4	t_5	t_6	t_7
Set A	$\boldsymbol{S_1}$	1	5	10	20	20	20	20
	$\boldsymbol{S_2}$	1	5	10	25	25	25	25
	$\boldsymbol{S_3}$	1	5	10	30	30	30	30
	$\boldsymbol{S_4}$	1	5	10	45	45	45	45
	$\boldsymbol{S_5}$	5	10	25	75	75	75	75
	$\boldsymbol{S_6}$	10	25	50	100	100	100	100
Set C	$\boldsymbol{S_1}$	1	1	1	1	1	1	1
	$\boldsymbol{S_2}$	1	10	10	10	10	10	10
	$\boldsymbol{S_3}$	1	10	30	30	30	30	30
	$\boldsymbol{S_4}$	1	10	30	60	60	60	60
	$\boldsymbol{S_5}$	1	10	30	60	100	100	100
	$\boldsymbol{S_6}$	1	10	30	60	100	140	140

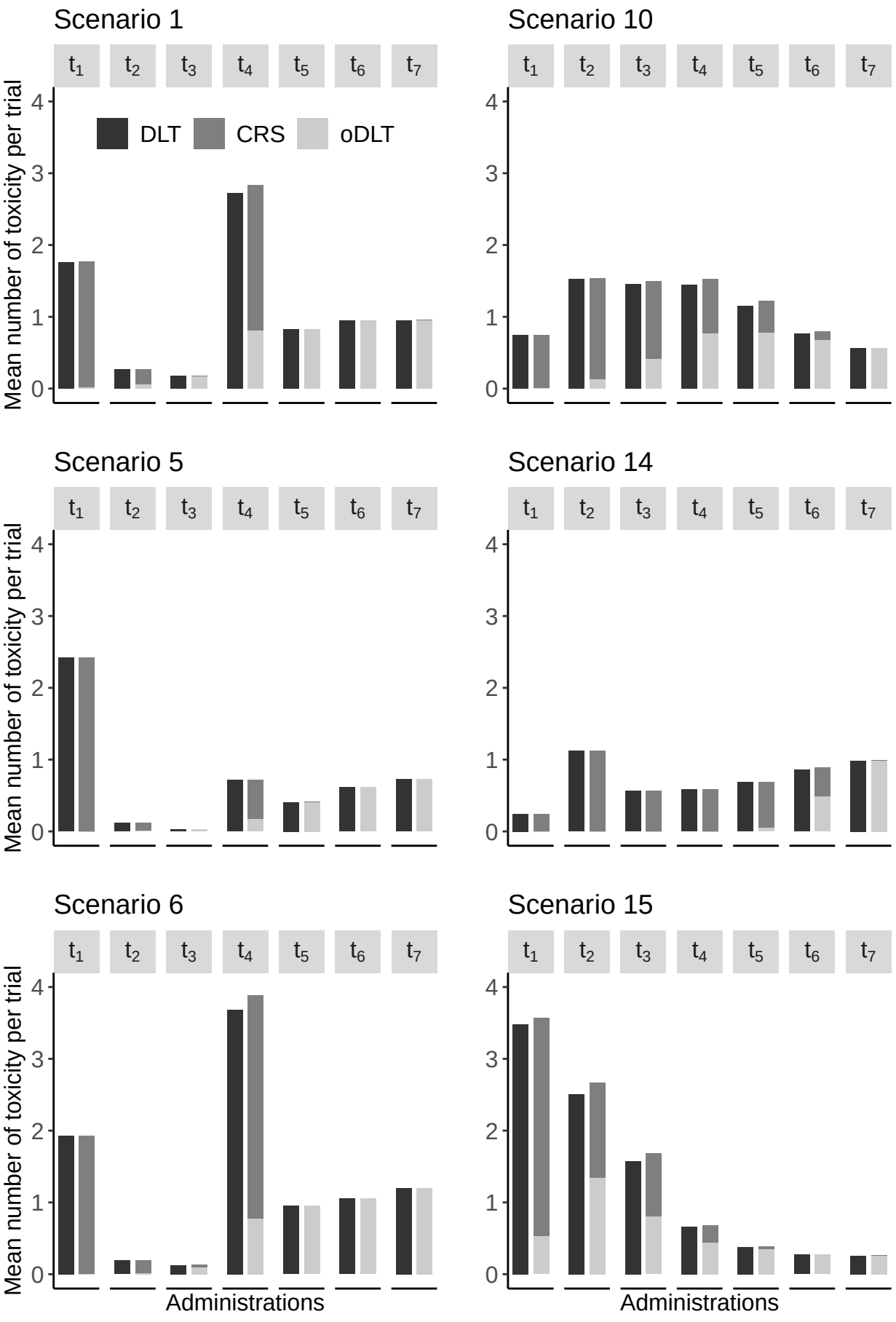

Figure 9: Mean number of DLT, CRS and DLT_o per trial for each of the seven administrations of the dose regimens observed in Scenarios 1, 10, 5, 14, 6, 15. Scenarios 1, 5 and 6 (Sets A and B) have similar probabilities of toxicities than Scenarios 10, 14, and 15 (Set C), respectively.

Table 9: Proportions of selecting each dose regimen as the MTD-regimen over the 1000 trials in the six toxicity scenarios defined on Set C. For each scenario, the marginal probabilities of DLT, CRS and DLT_o are defined, and the association between the CRS and DLT_o is represented by the average risk ratio (RR). Results are presented for the 3 joint approaches (DRtox_indep, DRtox_copula and DRtox_cond) and the logistic CRM. The proportions of correct selection (PCS) of the MTD-regimen are represented in bold.

Scenario	Set	RR	Method		S_1	S_2	S_3	S_4	S_5	S_6
10	C	1.89		p_T	0.03	0.09	0.18	**0.30**	0.45	0.57
				$p_T^{(1)}$	0.03	0.08	0.12	**0.18**	0.26	0.36
				$p_T^{(2)}$	0.00	0.01	0.07	**0.17**	0.31	0.41
			DRtox_indep		0	1	37	**51**	9	2
			DRtox_copula		0	1	26	**55**	16	3
			DRtox_cond		0	1	36	**51**	9	2
			Logistic CRM		0	1	19	**51**	23	6
11	C	6.37		p_T	0.04	0.10	0.18	**0.30**	0.45	0.58
				$p_T^{(1)}$	0.04	0.10	0.15	**0.22**	0.33	0.46
				$p_T^{(2)}$	0.00	0.01	0.06	**0.22**	0.41	0.55
			DRtox_indep		0	2	47	**46**	5	1
			DRtox_copula		0	1	32	**56**	10	2
			DRtox_cond		0	2	40	**50**	7	1
			Logistic CRM		0	1	19	**53**	23	4
12	C	5.84		p_T	0.02	0.09	0.18	**0.30**	0.42	0.52
				$p_T^{(1)}$	0.02	0.08	0.12	**0.17**	0.25	0.34
				$p_T^{(2)}$	0.00	0.02	0.11	**0.27**	0.41	0.51
			DRtox_indep		0	2	43	**42**	10	3
			DRtox_copula		0	1	31	**48**	14	6
			DRtox_cond		0	1	36	**48**	12	4
			Logistic CRM		0	0	19	**45**	26	10
13	C	1.94		p_T	0.04	0.11	0.19	**0.30**	0.45	0.61
				$p_T^{(1)}$	0.04	0.10	0.17	**0.24**	0.36	0.51
				$p_T^{(2)}$	0.00	0.01	0.04	**0.10**	0.19	0.28
			DRtox_indep		0	3	45	**46**	5	0
			DRtox_copula		0	2	36	**51**	10	1
			DRtox_cond		0	3	45	**46**	5	0
			Logistic CRM		0	2	20	**53**	21	4
14	C	1.99		p_T	0.01	0.05	0.08	0.11	0.18	**0.30**
				$p_T^{(1)}$	0.01	0.05	0.08	0.10	0.14	**0.18**
				$p_T^{(2)}$	0.00	0.00	0.00	0.00	0.04	**0.17**
			DRtox_indep		0	0	0	9	32	**59**
			DRtox_copula		0	0	0	5	25	**70**
			DRtox_cond		0	0	0	9	32	**59**
			Logistic CRM		0	0	0	2	20	**77**
15	C	1.82		p_T	0.16	**0.30**	0.44	0.57	0.75	0.88
				$p_T^{(1)}$	0.11	**0.17**	0.28	0.42	0.66	0.83
				$p_T^{(2)}$	0.06	**0.18**	0.26	0.33	0.41	0.47
			DRtox_indep		14	**72**	13	0	0	0
			DRtox_copula		10	**69**	20	1	0	0
			DRtox_cond		14	**72**	14	0	0	0
			Logistic CRM		14	**56**	27	2	0	0

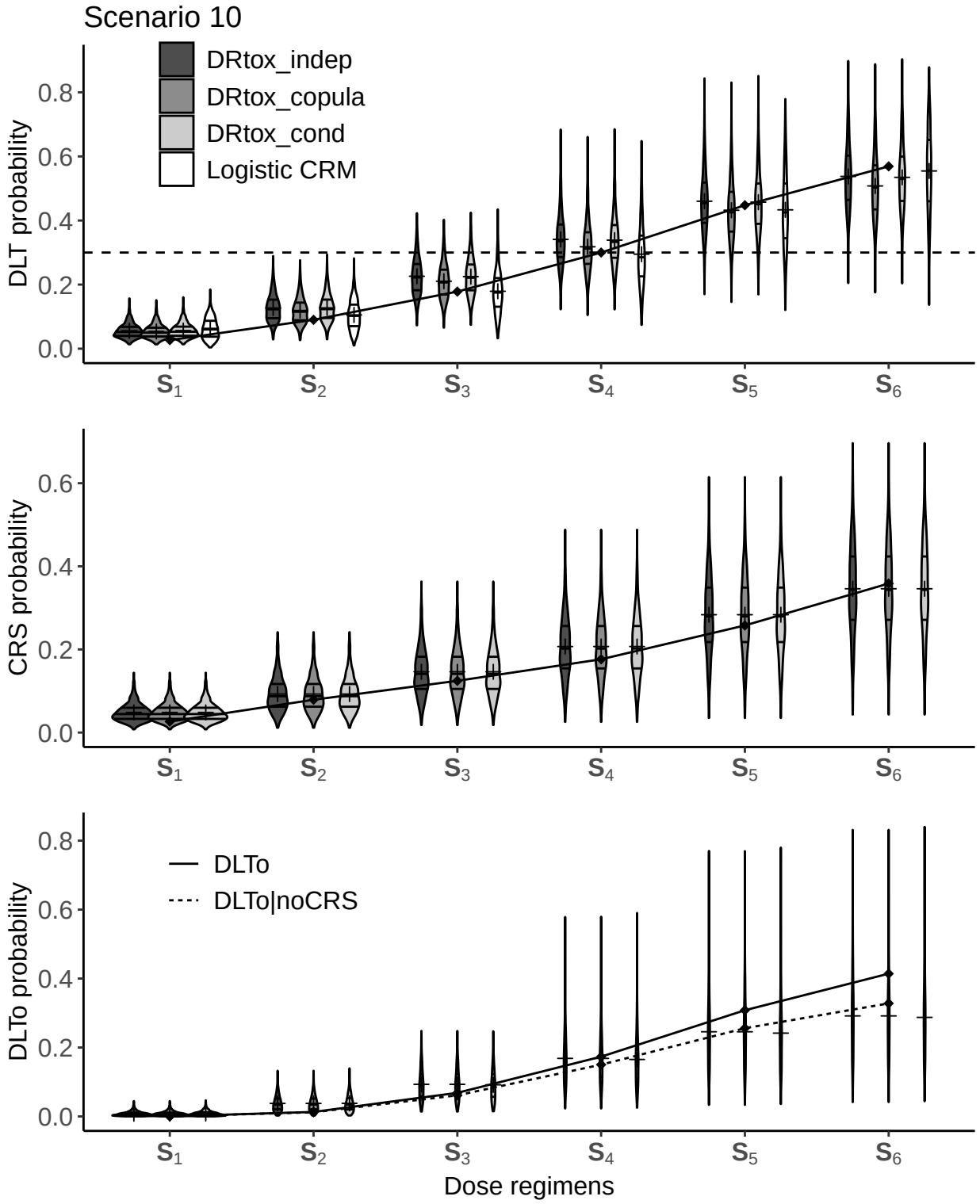

Figure 10: Violin plots of the estimated probabilities of DLT, CRS and DLT_o in Scenario 10 for 1000 simulated trials. All three joint approaches and the CRM estimate the probability of DLT in the first part of the figure, where the dashed line represents the toxicity target and the solid line represents the true DLT probabilities. Our three joint approaches estimate the probability of CRS with the logistic DRtox in the second part of the figure, where the solid line represents the true CRS probabilities. In the last part of the figure, both the DRtox_indep and DRtox_copula estimate the marginal probability of DLT_o while the DRtox_cond estimates the conditional probability of DLT_o given no CRS has occurred. The solid line represents the true marginal probabilities of DLT_o while the dotted line represents the true conditional probabilities of DLT_o given no CRS. In all the figure, horizontal lines on the density estimates represent the median and first and third quantiles of the distributions, and the plus sign represents the mean.