Bayesian Curve-Free Dose-Finding Design for VENETIAN Trial.

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Setting

Consider a combination trial in which a combination of chemotherapy (the standard of care) and a re-purposed drug are studied. The dose of the chemotherapy is fixed and there are *three* doses of the re-purposed drug: the starting dose d_0, the de-escalated dose d_{-1}, and escalated dose d_1.

The objective of the trial is to find the highest safe dose and recommend it for the subsequent Phase 2 study. Given a recently completed trial on the chemotherapy administered as a monotherapy and the dose-limiting toxicity (DLT) definition to be used in the VENETIAN trial (excluding likely reversible chemotherapy related Grade 3 toxicities), the DLT rate for the monotherapy alone is expected to be around 17%. An increase of 5 – 10% over this value in the combination trial in the studied patient population would be deemed acceptable. This translates into the *upper toxicity bound* in the VENETIAN trial to be 27%, denoted by $\gamma = 0.27$. The objective of the trial is to identify the highest acceptable dose – the highest dose with the toxicity risk below 27%.

Design

A curve-free (also referred to as model-assisted) Bayesian design developed by Gasparini and Eisele (2000); Mozgunov et al. (2020) is proposed. The choice of this design for the considered trial is predicated by the following factors:

1. The design models toxicity rate at the starting combination as a Beta random variable that allows for the natural, straighforward, and flexible incorporation of the historical information that is available for this trial. Additionally, the use of external information for this design is studied in the literature (Mozgunov et al., 2020) while not covered as much for other model-assisted designs.

2. In contrast to other alternative model-assisted designs (e.g., mTPI and BOIN), the curve-free design allows for modelling of the whole dose-toxicity relationship and therefore borrows information between the doses. This can result in more efficient use of information – DLT/no DLT response at a given dose will inform the estimated toxicity rates at other doses.

The design is adjusted for the de-escalation nature of the study.

Let p_0, p_{-1} and p_1 be the probabilities of a DLT at the starting combination d_0, lower combination, and higher combination, respectively. The probability at the starting combination has a Beta prior distribution with parameters $\mathcal{B}(t_1, t_2)$. Let θ_{-1} be the "link" between the lower combination d_{-1} that reflects by what percentage the risk toxicity is decreased when de-escalating the dose, and let θ_1 be the "link" between the higher combination d_1 and starting combination that reflects by what percentage the risk toxicity is increased when escalating the dose.

Formally,

$$\theta_{-1} = \frac{p_{-1}}{p_0}, \quad \theta_1 = \frac{1 - p_1}{1 - p_0}$$

and they have prior Beta distributions with parameters

$$\theta_{-1} \sim \mathcal{B}(t_3 \times t_4, (1 - t_3) \times t_4), \quad \theta_1 \sim \mathcal{B}(t_5 \times t_4, (1 - t_5) \times t_4)$$

where $0 \leq t_3 \leq 1$ is expected decrease in the mean toxicity from decreasing the dose, $0 \leq t_5 \leq 1$ is expected increase in the mean toxicity from increasing the dose, and $t_4 \in \mathbb{R}_+$ is the strength of the prior. Then the probability at the lower and higher combinations can be written as

$$p_{-1} = p_0 \times \theta_{-1}, \quad p_1 = 1 - \theta_1(1 - p_0)$$

which are the products of Beta distributions. This form of the model allows for the assumption of monotonicity (where it is assumed that the toxicity risk escalates from d_{-1} to d_0, and further for d_1), which allows the borrowing of information across combinations; furthermore, prior data at the starting combination from previous research can be incorporated for further efficiency.

After the DLTs for the previous cohort of patients are evaluated, the posterior distributions of the risk of toxicity at each combination are updated using Bayes' Theorem and the decision on the next cohort allocation is made based on the proposed model. The design takes the following form:

1. The cohort of 3 patients is assigned to combination d_0
2. After the DLTs for the previous cohort are evaluated, the posterior distribution of the toxicity risk at each combination are updated.
3. The set of the safe combinations is determined; the combination is deemed to be safe if

$$\mathbb{P}\left(p_j > 0.27\right) < c_{overdose} \tag{1}$$

   where $c_{overdose}$ is the probability threshold that controls the overdosing of the patients.
4. The next cohort of patients is assigned to the highest safe combination.
5. Steps 2–4 are repeated until the maximum number of patients is reached.

The quantities in Equation (1) define the properties of the design (together with the prior distribution) and can be tuned/calibrated to achieve the desirable balance between the probability of correct selections under various scenarios. Its calibration together with setting up the prior is given below.

Setting Up Prior and Design Parameters

The design as specified above requires specification of the prior distribution parameters, t_i ($i = 1, ..., 5$), and the overdosing threshold for the decision making in Equation (1).

Prior Distributions for the Starting Combination

Concerning the prior, the parameters of the Beta distribution for the starting combination, t_1, t_2, are specified using historical information. Specifically, the team is a-priori certain that the toxicity risk at this combination will be greater than for the population for which the previous data are available. This will be written as a probabilistic statement involving Beta random variables. The original historical data are based on 354 patients. Modifying the definition of the DLT as used in the proposed trial, i.e., excluding likely reversible chemotherapy related Grade 3 toxicities, we assume that 17% of patients experienced DLTs satisfying such our definition (60 DLTs out of 354 patients).

Let $P_{previous}$ be the toxicity risk at the chemotherapy given alone in the previously considered patients population. Then, one knows that

$$\mathbb{P}\left(p_0 > P_{previous}\right) > \eta$$

where η is a probability threshold. Intuitively, this statement can be understood as "we are η% certain that the risk of toxicity at the starting combination, p_0, is greater than $P_{previous}$". To induce a sufficient amount of uncertainty in the underlying distribution one can vary η to obtain prior distribution for p_0. We choose $\eta = 0.80$ implying that the clinicians are very certain that the toxicity risk higher (while allowing for uncertainty in the probability itself). We also require that the prior mean is below the upper toxicity bound of 27%. Then, we select *the least informative prior* satisfying these two constraints - this is done via a grid search for various values of t_1 and t_2. The following distribution was found

$$p_0 \sim \mathbb{B}(5.0, 16.2).$$

Note that this prior distribution corresponds to the strength of prior equivalent to around 21 patients. We feel this is a justifiable prior given the large amount of data available in the previous study (354 patients in the historical data) and that the clinicians are fairly confident that the toxicity risk in this trial will be higher.

Prior Parameters for the Link Functions and Overdose Threshold

The prior parameters for the link functions and $c_{overdose}$ were obtained by their simultaneous calibration over four scenarios (see section Numerical Evaluation). Specifically, we have used grid search of

$$t_3, t_5 \in \{0.75, 0.775, 0.80, 0.825, 0.85, 0.875, 0.90, 0.925, 0.95\},$$

$$t_4 \in \{2, 2.5, 3, 3.5, 4, 4.5, 5\},$$

$$c_{overdose} \in \{0.50, 0.525, 0.55, 0.575, 0.60, 0.625, 0.650, 0.675\}.$$

The combinations parameters that resulted in a high proportion of correct conclusions across all four scenarios was selected. The following prior for the link was used

$$\theta_{-1} \sim \mathbb{B}(0.75 \times 3, (1 - 0.75) \times 3);\ \theta_1 \sim \mathbb{B}(0.90 \times 3, (1 - 0.90) \times 3),$$

and the overdosing threshold of $c = 0.55$.

Numerical Evaluation

Simulation Study

A simulation study studying the performance of the proposed design with specified parameters was conducted. We consider four scenarios: (i) with all doses being safe; (ii) with the escalating dose being unsafe; (iii) with the starting dose being unsafe, and (iv) all doses being unsafe. We study the proportion of each dose selection and the proportion of times the trial was terminated. We study 3 sample sizes $N = 18, 24, 30$ to explore how the operating characteristics change with the number of patients enrolled in the study. A cohort size of 3 patients is used, chosen based on how many patients the clinical team were happy to recruit before formally reviewing safety data and making escalation/de-escalation decisions.

For comparison, we include results for the 3+3 design (with a maximum sample size of $N = 18$).

	d_{-1}	d_0	d_1	Terminated	Safe Selected
Scenario 1: All safe					
Toxicity Risk	0.17	0.195	**0.22**		
3 + 3 Design	23%	18%	**36%**	23%	77%
Proposed Design ($N = 18$)	8%	35%	**56%**	2%	98%
Proposed Design ($N = 24$)	7%	34%	**58%**	1%	99%
Proposed Design ($N = 30$)	6%	32%	**59%**	2%	98%
Scenario 2: Only two are safe					
Toxicity Risk	0.17	**0.22**	0.37		
3 + 3 Design	26%	**33%**	18%	23%	59%
Proposed Design ($N = 18$)	12%	**58%**	28%	2%	70%
Proposed Design ($N = 24$)	14%	**62%**	21%	3%	76%
Proposed Design ($N = 30$)	13%	**65%**	18%	3%	78%
Scenario 3: Only one is safe					
Toxicity Risk	**0.22**	0.37	0.47		
3 + 3 Design	**43%**	19%	5%	34%	43%
Proposed Design ($N = 18$)	**44%**	39%	6%	44%	11%
Proposed Design ($N = 24$)	**52%**	28%	3%	16%	52%
Proposed Design ($N = 30$)	**54%**	26%	2%	19%	54%
Scenario 4: None are safe					
Toxicity Risk	0.37	0.47	0.57		
3 + 3 Design	28%	7%	1%	**64%**	–
Proposed Design ($N = 18$)	36%	14%	1%	**49%**	–
Proposed Design ($N = 24$)	30%	7%	0%	**63%**	–
Proposed Design ($N = 30$)	25%	4%	0%	**71%**	–

Table 1: The proportion of each combination selection under 3 considered scenarios. The proportion of correct selection is in **bold**. Results are based on 5000 simulations.

Under all considered scenarios, for the sample size of $N = 24$, the design can reach the right conclusions with probability of 52%–63%. The highest proportion of correct conclusions can be achieved under the scenario 4 in which 63% of trial are correctly terminated earlier. Importantly,

the moderate percentages of correct conclusions across the scenarios can be explained by the difficulty of the dose-toxicity scenarios being considered: the historical data suggest that the lowest dose will have at least 17% and the upper toxicity bound is 27% - leaving just 10% "window" of acceptable doses. At the same time, the safe combination is selected with probability 52% – 99% depending on the scenario.

Comparing the performance to the 3+3 design, the proposed design noticeably outperformed 3+3 in all considered scenarios - the difference between the proportion of correct selections are between 9% – 22% under scenarios 1–3 and the same proportion of termination under the unsafe scenario 4.

Under the lower sample size, the proportion of correct conclusions decrease in all scenarios: under the considered scenarios, the proportion of right conclusion decreases by 2% – 14% if $N = 18$ is used. The proportion of correct conclusions increase by 1% – 8% if $N = 30$ is used, representing a very modest gain for the additional sample size (particularly when considering the subsequent increase in study length and cost).

Overall, given the trade-off between the sample size and the accuracy, via discussion with the clinical team, it was concluded that $N = 24$ results in an acceptable balance in the accuracy/safety for the required costs.

Individual Trial Behaviour

Additional to the simulation study, we also assess the individual trial behaviour of the design to ensure that after 0, 1, and 2 DLTs the recommendation of the model is intuitive and is in line with the clinicians' expectations. As can be seen below, the design leads to intuitive decision-making for the first cohort of patients.

0 DLTs at the Starting Combination

	d_{-1}	d_0	d_1
Probability of Overdose $\mathbb{P}(p > 0.27)$	8%	21%	46%

The recommendation is to escalate to d_1.

1 DLT at the Starting Combination

	d_{-1}	d_0	d_1
Probability of Overdose $\mathbb{P}(p > 0.27)$	17%	37%	60%

The recommendation is to stay on the starting dose to d_0.

2 DLTs at the Starting Combination

	d_{-1}	d_0	d_1
Probability of Overdose $\mathbb{P}(p > 0.27)$	27%	56%	74%

De-escalate to dose d_{-1}.

Informative Prior vs Non-informative Prior

The results of the design performance above are based on the prior distribution for the starting combination that is informed by the existing clinical knowledge and expectation on the combination performance. Specifically, it is clinically expected that the studied combinations will result in toxicity rates of at least 17% as the backbone agent alone results in 17% of patients, based on the recent completed trial with 354 patients. Given that this knowledge is closely relevant to the trial in question, it might be suboptimal (or even unethical) to completely ignore it. Instead, using this information (while accounting for the uncertainty coming from it) can contribute to more meaningful toxicity estimates (as it informs a range of its clinically expected values) and more meaningful escalation decisions.

At the same time, the proposed design

- Uses the *least informative* prior on the starting combination subject to the high confidence that it will have toxicity rate above the risk associated with backbone agent administered as a monotherapy (accounting for the uncertainty in the external data via Bayesian inference) and that its toxicity risk is below the upper toxicity bound of 27%.
- Uses weakly informative (operational) prior distribution for the dose-toxicity relationship.
- Has good operating characteristics across all scenarios, including high-toxic scenarios, i.e., it safeguards the patients.

To support these arguments, below we provide the comparison of the design with the proposed parameters (refer to as "Informed Prior") and the design with weakly informative prior distributions (refer to as "WIP"). For fairer comparison, we calibrate the parameters for WIP similarly to the proposed design with the exception that we additionally calibrate the strength of the prior distribution on the starting combination (rather than it being informed by the external data) with the same prior toxicity mean of just under the upper toxicity bound of 27%.

The following prior parameters for the WIP are used:

$$\theta_{-1} \sim \mathbb{B}(0.575\times5, (1-0.575)\times5);\ \theta_0 \sim \mathbb{B}(0.235\times5, (1-0.235)\times5);\ \theta_1 \sim \mathbb{B}(0.875\times5, (1-0.875)\times5),$$

and the overdosing threshold of $c = 0.625$.

Estimates under informed and weakly-informative priors

To support the argument of more clinically aligned prior distribution for the stating combination, we review the WIP performance. Firstly, under the weakly-informative parameters, the prior distribution implies that the probability of the toxicity risk at the starting combination being below 17% (the most likely value for the backbone agent administered as a monotherapy) is around 44%, implying that it is nearly as likely as being above 17%. This compares to 25% for the informed prior which more closely reflect the clinical expectations and historical knowledge.

Furthermore, consider a hypothetical scenario in which 0/3 DLTs are observed for the first cohort of patients in the trial; while the recommendation under both design specifications will be to escalate the dose, the designs will result in different estimates of the toxicity risks - see Table 2.

Mean Toxicity Estimates after 0/3 at d_0	d_{-1}	d_0	d_1
Informed Prior	15%	20%	28%
Weakly Informative Prior	8%	15%	25%

Table 2: The point estimates under informed prior and WIP after 0/3 DLTs were observed in the first cohort at the starting combination d_0.

The weakly informative prior implies that, after the first cohort, the estimated toxicity is 15%, which is below the most likely value of the monotherapy risk. Furthermore, this design also suggests 8% risk for the d_{-1}, which is far below the expected value of toxicities. Hence, the weakly informative prior leads to toxicity estimates that are not aligned with the clinical expectation and clinical knowledge. At the same time, both are recognised to be an integral part of efficient implementation of advanced adaptive designs in practice (Yap et al., 2017).

Comparison Via Simulations

Furthermore, we perform a simulation study of the informed and WIP designs to evaluate their performance on average and under various clinically possible scenarios. The comparison is done under the selected sample size of $N = 24$. The results are given in Table 3.

	d_{-1}	d_0	d_1	Terminated	Mean DLT rate
Scenario 1: All safe					
Toxicity Risk	0.17	0.195	**0.22**		
Informed Prior	6.8%	32.0%	**59.6%**	1.6%	20.9%
Weak	12.8%	23.3%	**61.9%**	2.1%	21.0%
Scenario 2: Only two are safe					
Toxicity Risk	0.17	**0.22**	0.37		
Informed Prior	14.0%	**63.4%**	20.4%	2.2%	26.4%
Weak Informative Prior	20.9%	**53.5%**	23.1%	2.5%	26.5%
Scenario 3: Only one is safe					
Toxicity Risk	**0.22**	0.37	0.47		
Informed Prior	**50.2%**	31.7%	3.1%	15.2%	34.2%
Weak Informative Prior	**58.2%**	24.2%	3.4%	14.2%	33.7%
Scenario 4: None are safe					
Toxicity Risk	0.37	0.47	0.57		
Informed Prior	31.0%	7.2%	0.0%	**61.6%**	46.8%
Weak Informative Prior	35.3%	4.9%	0.0%	**59.7%**	47.7%
Mean Accuracy for Informed Prior		58.5%			
Mean Accuracy for WIP		58.2%			

Table 3: The proportion of each combination selection under four considered scenarios for $N = 24$. The proportion of correct selection is in **bold**. Results are based on 5000 simulations.

Firstly, on average, both design specifications result in nearly the same average accuracy across

all considered scenarios (just under 60%), but with some differences within the individual scenarios. Under Scenario 1, while both versions recommend the right dose with probability of around 60%, the informed prior recommends dose d_0 nearly 9% more often. It means that even if the correct dose is not accurately chosen, the informed prior has a higher chance of selecting the next best dose, which should lead to a higher chance of success in later phases. Under Scenario 2, the proportion of the correct selection is 10% higher under the informed prior, with LOWER chance of selecting an overly toxic dose. The advantage of the informed prior goes with the cost of being outperformed by the WIP under Scenario 3 by 8%, and higher proportion of over-toxic selections (albeit with a very similar chance of selecting the most toxic dose). At the same time, the mean DLT rate (i.e., average number of patients that are expected to experience a DLT event during the trial) is the same. Under Scenario 4, the designs perform similarly, with approximately 60% of trials correctly terminated.

Overall, the informed prior results in the same or better characteristics under 3 out of 4 scenarios with no costs in terms of the mean number of DLTs observed. Given that the clinical team is primarily expecting to observe scenario 1 or scenario 2, and the proposed design safeguards patients under more toxic scenarios 3 and 4 (the toxicity profiles of which could be also picked up by further tolerability data beyond DLT/no DLT used by the model), the informed prior is a preferred option. Together with more clinically meaningful estimates obtained using the proposed prior and more efficient use of (closely relevant) external information, the informed prior is selected for the proposed trial.

References

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