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 will also 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 at the starting combination d_0, lower combination and higher combinations, respectively. The probability at the starting combination d_0 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 dose, and

let θ_1 be the "link" between the higher combination d_1 and starting combinations 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, where $0 \leq t_5 \leq 1$ 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 has a product of Beta distribution. This form of the model will allow to benefit from the monotonicity assumption (one knows that the toxicity risk at d_{-1} is less and d_1 is more), will allow to borrow information between combinations, and will allow to benefit from the known prior data at the starting combination.

Then, 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 the Bayes Theorem and the decision on the next cohort allocation is made based on the proposed model. Then, 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 combination. The combination is estimated 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_1, t_2, t_3, t_4, t_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 (higher) combinations, t_1, t_2 are specified using the 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 the 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 that reflects a 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 conclusion 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 is 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 selections 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. The cohort size of 3 patients is used.

For the comparison, we include 3+3 design (for the 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 conclusion go down under all scenarios. Under considered scenarios, the proportion of right conclusion decreases by 2% – 14% if $N = 18$ is used. Under higher sample size, the proportion of correct conclusions increase by 1% – 8% if $N = 30$ is used.

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 intutitive and is in line with the clinicians' expectations. As can be seen below, the design leads to intuitive decision-makin 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}.

References

Gasparini, M. and Eisele, J. (2000) A curve-free method for phase I clinical trials. *Biometrics*, **56**, 609–615.

Mozgunov, P., Gasparini, M. and Jaki, T. (2020) A surface-free design for phase i dual-agent combination trials. *Statistical Methods in Medical Research*, 0962280220919450.