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Supplementary Information for 'A Decision-Theoretic Phase I-II Design for Ordinal Outcomes in Two Cycles'

1. Practical Guidelines for a Design Using Utility Functions

Getting a design accepted for an actual protocol: In explaining the proposed design to the physicians planning a two-cycle dose-finding trial, and possibly later to reviewers on Institutional Review Boards or members of federal regulatory agencies such as the US FDA or NIH, several key advantages of using a utility function can be emphasized. These include design features discussed in detail in the simulations of the main text. We reiterate them in non-technical language that can be understood easily by non-statisticians.

1. *The advantage of using efficacy as well as toxicity, summarized by their joint utility, rather than toxicity alone to characterize patient outcome.* A simple example is given in Table 1, where doses 1 and 2 have nearly identical marginal toxicity probabilities, but dose 2 is greatly superior in efficacy, therefore boosting the utility of dose 2. In the example, assuming the utility in Table 1 of the main text, the expected utilities for doses 1 and 2 are 28.94 and 40.95, respectively, and dose 2 will be selected for patients. This advantage is already quite large with the more common single-cycle phase I-II designs when compared to phase I designs (Thall and Cook, 2004; Houede *and others*, 2010). For the two-cycle setting, Lee *and others* (2015) showed that a design using toxicity and efficacy based on their

Table 1. Example for the joint utility

Efficacy	Toxicity			Total
	Mild	Moderate	Severe	
PD	0.224	0.28	0.196	0.7
SD	0.032	0.04	0.028	0.1
PR/CR	0.064	0.08	0.056	0.2
Total	0.32	0.40	0.28	1.00

(a) Dose 1

Efficacy	Toxicity			Total
	Mild	Moderate	Severe	
PD	0.084	0.126	0.09	0.3
SD	0.056	0.084	0.06	0.2
PR/CR	0.14	0.21	0.15	0.5
Total	0.28	0.42	0.30	1.00

(b) Dose 2

joint utility performs better than methods using toxicity only.

2. *The advantage of using ordinal efficacy and toxicity, rather than binary variables obtained by dichotomization.* Dichotomization of ordinal outcome results in loss of information and efficiency, which is clearly seen in Figure 2 of the main text.

3. *The ability to optimally tailor the choice of a patient's cycle 2 dose based on both the patient's own cycle 1 data, as well as data from other patients.* This is reflected in the superior performance of the design, compared to existing methods, in terms of summary statistics such as those in Figure 3 of the main text.

Trial Conduct: Given the necessary computer program calculating outcome-adaptive decisions, the only additional practical requirements for implementing the proposed design in a real-life trial over existing adaptive single-cycle phase I designs, such as the CRM (Continuous Reassessment Method), are that (i) both toxicity and efficacy must be recorded, and (ii) two decisions must be made for each patient, that is, a decision for each of the two cycles.

Eliciting numerical utilities: Recall that $u_{\text{cycle}}(y_c, z_c)$ is the utility assigned to outcome (y_c, z_c) in each cycle $c = 1, 2$. To guide the physician(s) in the utility elicitation process, one first should establish the limiting utilities for the best and worst outcomes. In the example illustrated in the main text, we used 100 and 0 for the best and worst outcomes, respectively. It then should

be explained that $u_{\text{cycle}}(y_c, z_c)$ must decrease as the level of toxicity, y_c, becomes more severe and must increase as the level of efficacy, z_c, becomes more desirable. Once an initial numerical utility table has been established, using Table 1 of the main text for illustration, the physician(s) should be shown (i) numerical differences such as $u_{\text{cycle}}(Mild, PR/CR) - u_{\text{cycle}}(Mild, SD) = 100 - 70 = 30$ and $u_{\text{cycle}}(Moderate, PR/CR) - u_{\text{cycle}}(Moderate, SD) = 80 - 50 = 30$, or (ii) different outcomes with identical utilities such as $u_{\text{cycle}}(Severe, SD) = u_{\text{cycle}}(Mild, PD) = 25$, and asked if this is the intention. The physician(s) then may wish to modify their initial utilities on this basis.

2. Simulation Design

Recall that $J = K = 3$ and $m = 5$, and that $\tilde{d}$, $\tilde{Y}$ and $\tilde{Z}$ are rescaled versions of d, y and z, respectively. From §4.2, we determine joint probabilities by specifying the following conditional probabilities :

$$\begin{aligned} P(Y_1 = y_1, Z_1 = z_1, Y_2 = y_2, Z_2 = z_2 \mid d_1, d_2) = P(Y_1 = y_1 \mid d_1) P(Z_1 = z_1 \mid d_1, y_1) \\ P(Y_2 = y_2 \mid d_1, y_1, z_1, d_2) \\ P(Z_2 = z_2 \mid d_1, y_1, z_1, d_2, y_2). \end{aligned}$$

In the simulations, we use the following parametric models to generate the outcomes:

- $P(Y_1 \leqslant y_1 \mid d_1) = \Phi(\tilde{\xi}_{1,y_1}(d_1))$, where $\tilde{\xi}_{1,y_1}(d_1) = \bar{\xi}_{y_1}(d_1)$.
- $P(Z_1 \leqslant z_1 \mid d_1, y_1) = \Phi(\tilde{\eta}_{1,z_1}(d_1, y_1))$, where $\tilde{\eta}_{1,z_1}(d_1, y_1) = \bar{\eta}_{z_1}(d_1) + w_{1,1}\tilde{y}_1$.
- $P(Y_2 \leqslant y_2 \mid d_1, y_1, z_1, d_2) = \Phi(\tilde{\xi}_{2,u_2}(d_1, y_1, z_1, d_2))$, where $\tilde{\xi}_{2,j_2}(d_1, y_1, z_1, d_2) = \bar{\xi}_{y_2}(d_2) + w_{2,1}\tilde{d}_1 + w_{2,2}r^T(d_1, y_1) + w_{2,3}\tilde{z}_1$.
- $P(Z_2 \leqslant z_2 \mid d_1, y_1, z_1, d_2, y_2) = \Phi(\tilde{\eta}_{2,z_2}(d_1, y_1, z_1, d_2, y_2)$, where $\tilde{\eta}_{2,z_2}(d_1, y_1, z_1, d_2, y_2) = \bar{\eta}_{z_2}(d_2) + w_{3,1}\tilde{d}_1 + w_{3,2}\tilde{y}_1 + w_{3,3}r^E(d_1, z_1) + w_{3,4}\tilde{y}_2$.

$\bar{\xi}_j(d) = \Phi^{-1}(p_{d,j})$ and $\bar{\eta}_k(d) = \Phi^{-1}(q_{d,k})$ are defined in the main text where $p_{d,j} = P(Y \leqslant j \mid d)$ and $q_{d,k} = P(Z \leqslant k \mid d)$ are specified in Table 4 of the main text. Specification of the scenarios is completed by specifying numerical values of coefficients, $\boldsymbol{w} = (w_{1,1}, w_{2,1}, w_{2,2}, w_{2,3}, w_{3,1}, w_{3,2}, w_{3,3}, w_{3,4})$, r^T and r^E, which induce associations among the four outcomes (Y_1, Z_1, Y_2, Z_2). Association of d_1 with cycle 2 outcomes is induced through $w_{2,1}$ and $w_{3,1}$. For example, a positive value of $w_{1,1}$ implies that given that the most unfavorable toxicity outcome is observed in cycle 1, a favorable efficacy outcome in cycle 1 is less likely to be observed, where $\tilde{y}_1 \in \{-1, 0, 1\}$ for $J = 3$. Table 2 shows the assumed coefficients, $\boldsymbol{w}$, for the five scenarios. $r^T(d_1, y_1)$ defines the joint effect of d_1 and Y_1 on Y_2. To explain how $r^T(d_1, y_1)$ affects $P(Y_2 = j \mid d_1, Y_1, Z_1)$ through (d_1, Y_1), we first observe that d_1 affects $P(Y_2 = j \mid d_1, Y_1, Z_1)$ in three different ways: directly through $w_{2,1}$ and indirectly through $w_{2,2}$ and $w_{2,3}$. We assume that the outcome $Y_1 = 2$ with $d_1 = 1$ increases $P(Y_2 = 2 \mid d_1, Y)$ more than the outcome $Y_1 = 2$ at $d_1 = 5$ by letting $r^T(1, 2) = 1.0$ and $r^T(5, 2) = 0.1$. Similarly, $r^E(d_1, z_1)$ describes how d_1 and Z_1 jointly affect Z_2. Table 3 shows the assumed numerical $r^T(d_1, y_1)$ values. The same values are assumed for $r^E(d_1, z_1)$.

Table 2. Assumed coefficients ($\boldsymbol{w}$) for the simulation scenarios

Scenario	Z_1	Y_2			Z_2			
	$w_{1,1}$	$w_{2,1}$	$w_{2,2}$	$w_{2,3}$	$w_{3,1}$	$w_{3,2}$	$w_{3,3}$	$w_{3,4}$
1	0.70	-0.20	-1.50	0.01	-0.03	1.80	-0.10	0.50
2	0.20	-0.03	-1.20	1.30	-0.13	1.50	-1.80	0.30
3	1.30	-0.20	-1.50	1.30	-0.03	1.80	-1.40	0.90
4	0.20	-0.03	-0.10	2.00	-0.13	0.20	-2.40	0.30
5	0.60	-0.08	-0.30	0.30	-0.10	0.30	-2.30	0.60
6	0.20	-0.25	-0.13	0.10	-0.12	0.10	-0.30	0.40
7	0.40	-0.10	-0.20	0.30	-0.10	0.50	-0.30	0.30
8	1.40	-0.20	-1.20	0.80	-0.40	0.50	-0.90	1.30

Table 3. $r^T(d_1, y_1)$, parameters which determine the joint effect of d_1 and y_1 on Y_2

d_1	Y_1		
	Mild (0)	Moderate (1)	Severe (2)
1	-0.1	0.2	1.0
2	-0.3	0.1	0.7
3	-0.5	0.0	0.5
4	-0.7	-0.1	0.3
5	-1.0	-0.2	0.1

3. Prior Calibration

We calibrate the hyperparameters $\tilde{\boldsymbol{\theta}} = (\sigma_Y^2, \sigma_Z^2, \tau^2, \rho, \bar{\boldsymbol{\beta}}_{x,c}, \Omega_{x,c})$, $x = u, v$ and $c = 1, 2$ using the notion of effective sample size (ESS) (Morita *and others*, 2008, 2012). We first obtain prior information about average behavior by eliciting mean values of $P(Y \leqslant y \mid d)$ for a chosen value of y at least three dose levels and $P(Z \leqslant z \mid d)$ for a chosen value of z at at least three dose levels. We the use these probabilities to determine values of the hyperparameters, τ^2, ρ, σ_Y^2, σ_Z^2 and $\bar{\boldsymbol{\beta}}_{x,c}$ with $\boldsymbol{\gamma}_1$ and $\boldsymbol{\gamma}_2$. We then specify $\Omega_{x,c}$ and generate pseudo samples of $\boldsymbol{\beta}_{x,c}$, for $x = u, v$, using the methodology described in Thall and Nguyen (2012, Section 4.3). We use the pseudo samples to generate samples of probabilities of interest using the specified hyperparameters, in particular, τ^2, ρ, σ_Y^2, σ_Z^2, $\boldsymbol{\gamma}_1$ and $\boldsymbol{\gamma}_2$. For example, we generate samples of $P(Y_1 = y_1 \mid d_1)$ for $y_1 = 0, \ldots, J-1$ implied by each of the pseudo samples of $\boldsymbol{\beta}_{x,c}$, $x = u, v$. We then approximate ESS with a Dirichlet distribution. Using $P(Y_1 = y_1 \mid d_1)$ as an example, we use the generated samples of $(P(Y_1 = 0), \ldots, P(Y_1 = J-1))$ for a dose level d_1 and approximate its distribution with a Dirichlet distribution. Specifically, we assume $(P(Y_1 = 0), \ldots, P(Y_1 = J-1)) \mid d_1 \sim \text{Dir}(\alpha_0, \ldots, \alpha_{J-1})$ with $s = \sum_{j=0}^{J-1} \alpha_j$ and estimate α_j and s. A Newton-Raphson method can be used to estimate α's and s Minka (2000). $\tilde{\boldsymbol{\theta}}$ can be calibrated such that the estimated s is not large and the estimated α's are close to each other. Continuing the example, we search for $\tilde{\boldsymbol{\theta}}$ such that the estimated values of α_j, $j = 0, \ldots, J-1$ are close while yielding a small value of s for any d_1. Any other probabilities can be used similarly for prior calibration, such as $P(Z_1 = z_1, Z_2 = z_2 \mid d_1, d_2)$ or

$P(Y_c = y_c, Z_c = z_c \mid d_c)$, $c = 1, 2$.

For the simulation studies given in the main text, the hyperparameter values were calibrated such that the ESSs are close to 1 for most of the quantities of interest, such as $P(Y_c)$, $P(Y_1, Y_2)$, $P(Y_c, Z_c)$. We first specified γ_y, $\boldsymbol{\gamma}_z$, σ_Y^2, σ_Z^2 and τ^2. Assumed probabilities of $Y = 0$ and of $Z = 0$ or 1 at three dose levels $d = 1, 3, 5$ were utilized to set $\boldsymbol{\gamma}_y = (-\infty, -2.0, 0.5, \infty)$, $\boldsymbol{\gamma}_z = (-\infty, -2.0, 0.0, \infty)$ and $\sigma_Y^2 = \sigma_Z^2 = \tau^2 = 2$. Those values were used to find ρ, $\boldsymbol{\beta}_{x,c}$ and $\Omega_{x,c}$, $x = u, v$ and $c = 1, 2$. The particular choice used for the simulations is; $\rho = -0.6$, for u_c, $\boldsymbol{\beta}_{u,c} = (-2.00, -0.58, 0.64)^t$, $\Omega_{u,c} = diag(9.5, 3, 2)$ $c = 1, 2$; for v_c, $\boldsymbol{\beta}_{v,c} = (-1.35, 0.99, -1.06)$, $\Omega_{v,c} = diag(9, 3, 2)$, $c = 1, 2$.

4. Comparison to Designs Obtained by Dichotomizing the Two Ordinal Outcomes to Obtain Two Binary Outcomes

To evaluate what may be gained by accounting for the ordinal outcomes, we consider four cases in which each 3-level ordinal toxicity and efficacy outcome was reduced to a binary variable. This mimics what is actually done in practice in order to use a design that requires binary efficacy and binary toxicity, and in this case the comparator is the design of Lee et al.(2015).

Two of the three levels of each of Y_c and Z_c were combined to define binary outcomes, $(Y_c^\star, Z_c^\star)$, for $Y_c^\star, Z_c^\star \in \{0, 1\}$ in the following four different ways :

- Binary Case 1:

$$Y_c^\star = \begin{cases} \text{Not toxic} & \text{if } Y_c = \text{ Mild or Moderate,} \\ \text{Toxic} & \text{otherwise,} \end{cases}$$

$$Z_c^\star = \begin{cases} \text{Not efficacious} & \text{if } Z_c = \text{ PD or SD,} \\ \text{Efficacious} & \text{otherwise} \end{cases}$$

Table 4. Assumed utilities for binary outcomes.

$Y_c^\star \backslash Z_c^\star$	No Eff.	Eff.
No Tox.	33.87	100
Tox.	0	48.39

(a) Case 1

$Y_c^\star \backslash Z_c^\star$	No Eff.	Eff.
No Tox.	23.33	100
Tox.	0	50

(b) Case 2

$Y_c^\star \backslash Z_c^\star$	No Eff.	Eff.
No Tox.	33.33	100
Tox.	0	55.56

(c) Case 3

$Y_c^\star \backslash Z_c^\star$	No Eff.	Eff.
No Tox.	25.00	100
Tox.	0	57.81

(d) Case 4

- Binary Case 2:

$$Y_c^\star = \begin{cases} \text{Not toxic} & \text{if } Y_c = \text{ Mild or Moderate,} \\ \text{Toxic} & \text{otherwise,} \end{cases}$$
$$Z_c^\star = \begin{cases} \text{Not efficacious} & \text{if } Z_c = \text{ PD,} \\ \text{Efficacious} & \text{otherwise} \end{cases}$$

- Binary Case 3:

$$Y_c^\star = \begin{cases} \text{Not toxic} & \text{if } Y_c = \text{ Mild,} \\ \text{Toxic} & \text{otherwise,} \end{cases}$$
$$Z_c^\star = \begin{cases} \text{Not efficacious} & \text{if } Z_c = \text{ PD or SD,} \\ \text{Efficacious} & \text{otherwise} \end{cases}$$

- Binary Case 4:

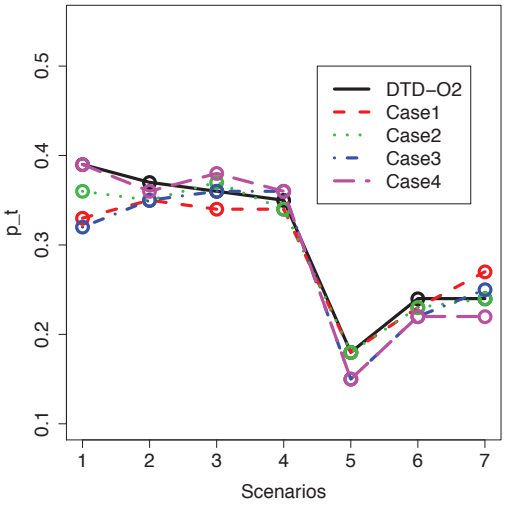
$$Y_c^\star = \begin{cases} \text{Not toxic} & \text{if } Y_c = \text{ Mild,} \\ \text{Toxic} & \text{otherwise,} \end{cases}$$
$$Z_c^\star = \begin{cases} \text{Not efficacious} & \text{if } Z_c = \text{ PD,} \\ \text{Efficacious} & \text{otherwise} \end{cases}$$

For each of the four binary cases, we find the utilities by taking an average of utilities associated with their original trinary outcomes and rescaling to make the minimum and maximum to be 0 and 100, respectively. The utilities with the binary outcomes are shown in Table 4.

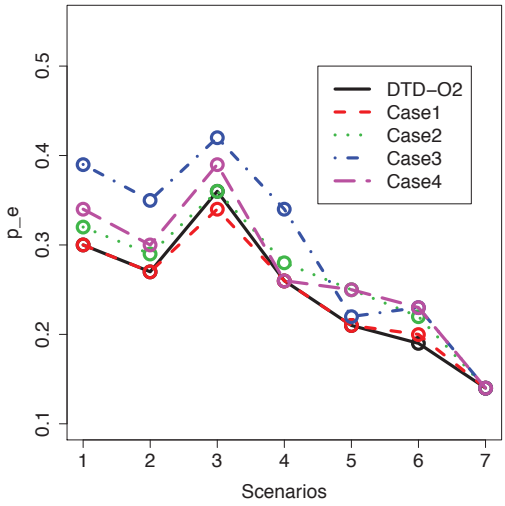
In addition to the comparison of DTD-O2 with the trinary outcomes to that with binary outcomes in §4.4 of the main text, we illustrate empirical probabilities of observing the outcomes, severe toxicity (p_t) and PD (p_e) in Figure 1. While p_t and p_e are close for DTD-O2 with the

trinary outcomes and with binary outcomes, binary case 3 is the most unfavorable as observed in Figure 2 of the main text. It is also due to many undesirable early terminations of trials.

Fig. 1. Plot of (p_t, p_e) for comparison to designs with binary outcomes where p_t and p_e are the probabilities of having $Y_{ic} = 2$ and $Z_{ic} = 0$, respectively. Note that smaller values are more desirable.



(a) p_t



(d) p_e

5. Additional Simulation Results for Comparison to the One-Cycle Designs SCC1 and SCC2

Recall that the single cycle designs SCC1 assumes no association between cycles and optimzies d_1 and d_2 separately, while SCC2 ignores cycle and treats cycle 1 and cycle 2 as if they were the same. In addition to the criteria $\bar{u}$, $\bar{U}_{trt}$ and U_{sel}, we evaluated the empirical toxicity and no efficacy rates for the two cycles, defined as follows. Let $\delta_{i,c} = 1$ if patient i was treated in cycle c and $\delta_{i,c} = 0$ otherwise. For each simulated trial with each method, we computed

$$p_t = \frac{\sum_{c=1}^{2}\sum_{i=1}^{n}\delta_{i,c}1(Y_{i,c} = J-1)}{\sum_{c=1}^{2}\sum_{i=1}^{n}\delta_{i,c}}$$

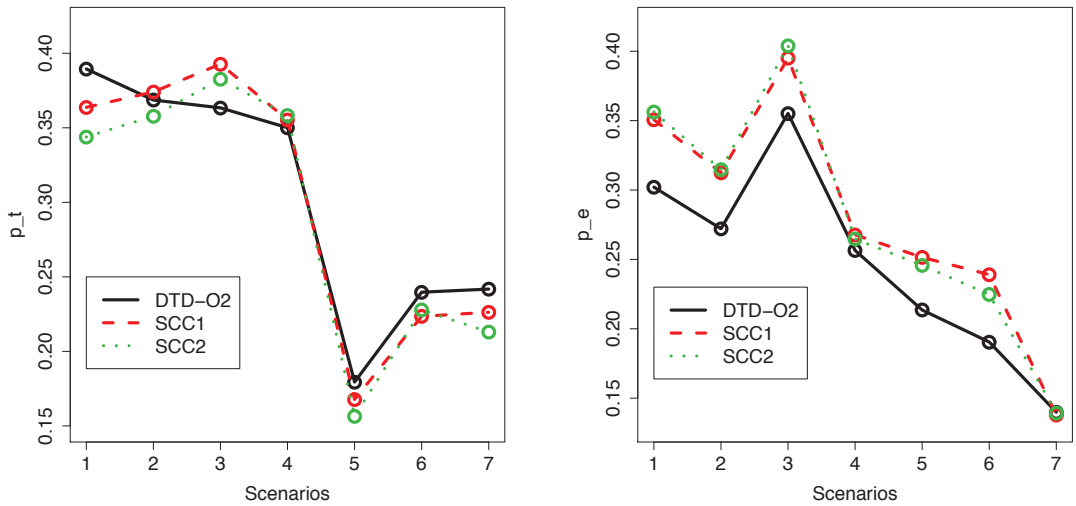
and

$$p_e = \frac{\sum_{c=1}^{2}\sum_{i=1}^{n}\delta_{i,c}1(Z_{i,c} = 0)}{\sum_{c=1}^{2}\sum_{i=1}^{n}\delta_{i,c}}.$$

Given these empirical probabilities of $Y_{i,c} = 2$(severe toxic) and $Z_{i,c} = 0$(SD) in each trial, for each scenario and method we computed the average of these values over the replicated trials. Smaller values of p_t and p_e are more desirable.

Figure 2 illustrates empirical probabilities of observing the severe toxicity (p_t) and the PD (p_e). In Scenarios 2 and 4, the proposed DTD-O2 yields smaller values for both p_t and p_e than the two competitors. For Scenarios 1, 3, 5 and 6, DTD-O2 assigns patients to possibly higher toxic but more efficacious treatments, eventually yielding more favorable results in $\bar{u}$, $\bar{U}_{trt}$ and U_{sel}, as described in §4.5 of the main text. The figure indicates the slightly poor performance of DTD-O2 in Scenario 7 as observed in Figure 3 of the main text.

Fig. 2. Plot of (p_t, p_e) for comparison to SCC1 and SCC2 where p_t and p_e are the probabilities of having $Y_{ic} = 2$(sever toxic) and $Z_{ic} = 0$ (PD), respectively. Note that smaller values are more desirable.



(a) p_t (d) p_e

6. Analysis of Sensitivity to λ

We studied the performance of the methods using different values of λ for Scenarios 2 and 5. Recall that λ is a design parameter used to discount cycle 2 expected utilities in computing total

utility to select d_1. Figures 3 and 4 illustrate $\bar{u}$, $\bar{U}_{trt}$, $U_{sel}(\boldsymbol{d}_{sel})$, p_t and p_e for $\lambda = 0.0, 0.4, 0.8, 1.0$ under each of the two scenarios. Note that $\bar{u}$ does not use λ but $\bar{U}_{trt}$ and $U_{sel}(\boldsymbol{d}_{sel})$ use λ. Also, SCC1 and SCC2 do not use λ to determine acceptable actions, their $\bar{u}$ stays constant over λ and their changes in $\bar{U}_{trt}$ and $\bar{U}_{sel}$ are only due to the change in λ. Results with $\lambda = 0.8$ has been used for comparisons. To show a complete comparison, the results with $\lambda = 0.8$ is included. Overall, λ does not change the relative performance among the methods much as indicated by $\bar{u}$ in the figures. It is observed that a small value of λ results in more early terminated trials under binary cases 1 and 3 (not shown). It may be because with a small value of λ, the decision of an early termination less counts cycle 2 outcomes and more relies on cycle 1 outcomes only and a trial is likely to be terminated even when unfavorable cycle 1 outcomes but favorable cycle 2 outcomes are observed in its early stage. Interestingly, $\bar{u}$ of binary case 3 improves as λ increases as shown in panel (a) of the figures, but relative performance by $\bar{U}_{trt}$ and $\bar{U}_{sel}$ becomes more inferior. This implies that under binary case 3, a trial is less likely to be terminated with a larger value of λ, leading to a larger $\bar{u}$ but this does not necessarily imply that the design makes a better decision.

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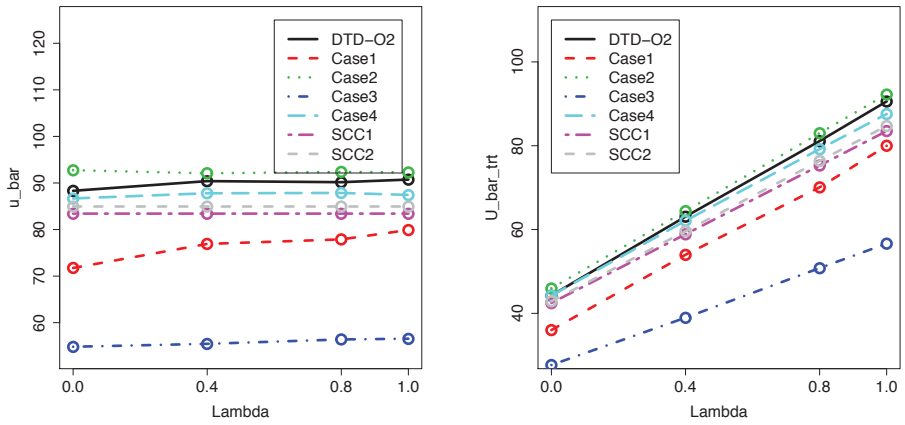
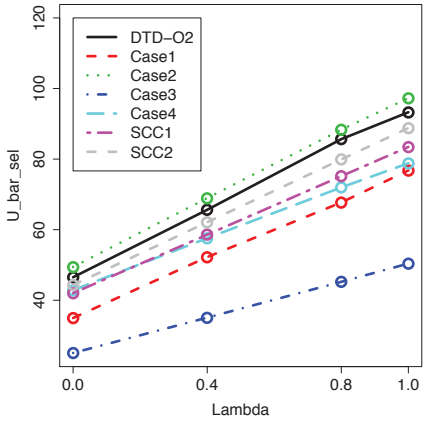
Fig. 3. [Scenario 2] Plot of $(\bar{u}, \bar{U}_{trt}, U_{sel}, p_t, p_e)$ with different values of $\lambda = 0.0, 0.4, 0.8, 1.0$.

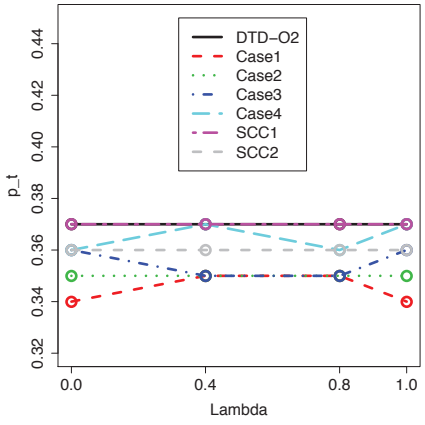


(a) $\bar{u}$

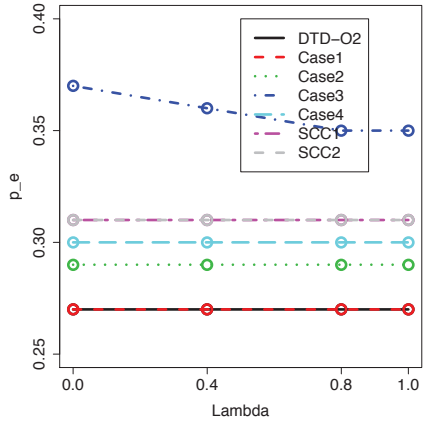
(b) $\bar{U}_{trt}$



(c) $\bar{U}_{sel}$

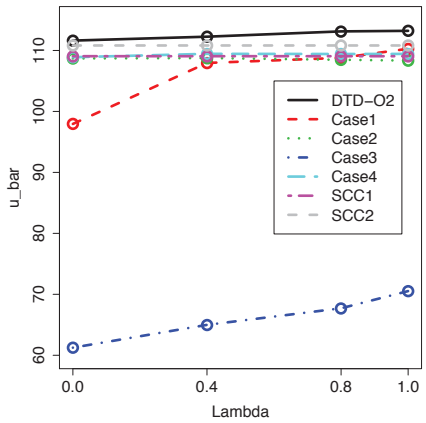


(d) p_t

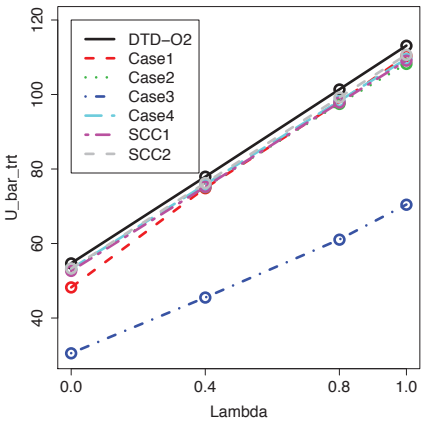


(e) p_e

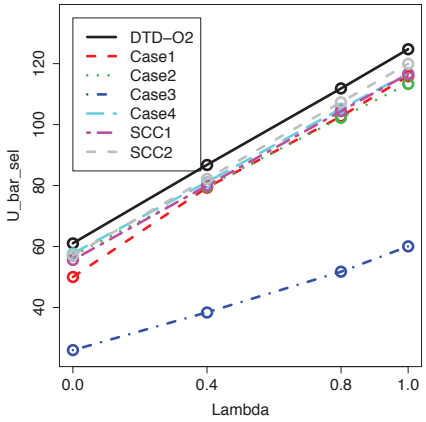
Fig. 4. [Scenario 5] Plot of $(\bar{u}, \bar{U}_{trt}, U_{sel}, p_t, p_e)$ with different values of $\lambda = 0.0, 0.4, 0.8, 1.0$.



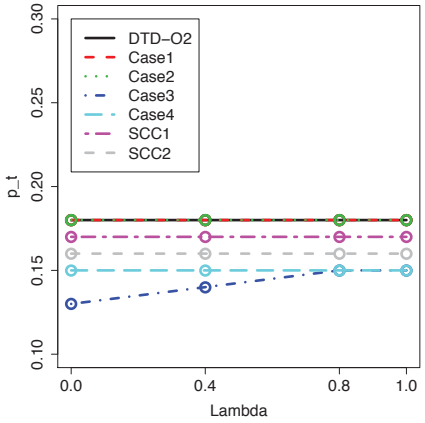
(a) $\bar{u}$



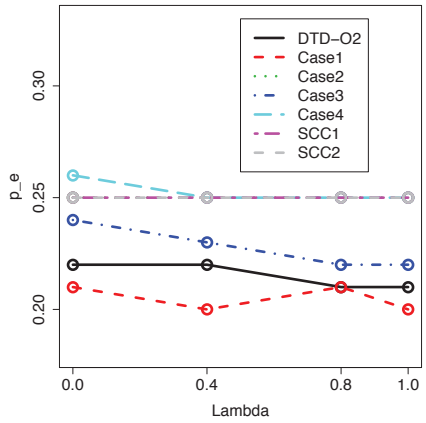
(b) $\bar{U}_{trt}$



(c) $\bar{U}_{sel}$



(d) p_t



(e) p_e