Web-based Supporting Material for

Phase I Design for Completely or Partially Ordered Treatment Schedules

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Table 1: *(1) Dose-schedule combination MTD selection (2) patient allocation (3) mean number of patients (4) % of DLT's induced and (5) % of trials stopped for safety for toxicity scenarios 1–7. These results present the operating charactistics of our proposed design for completely ordered schedules with the stopping rule described in Section 3.3 implemented. Combinations with DLT probabilities between 0.20 and 0.40 are in boldface.*

Scenario	Percent of combination selection			Percent of patient allocation			Mean # of patients	% DLT's	% stopped for safety
	0.10	**0.13**	**0.25**	**0.09**	**0.09**	**0.10**			
1	0.05	0.11	**0.15**	0.09	0.10	**0.11**	25.6	0.18	0.00
	0.01	0.04	0.11	0.06	0.08	0.10			
	0.00	0.00	0.04	0.05	0.05	0.08			
	0.13	0.07	0.00	**0.10**	0.06	0.00			
2	0.10	**0.21**	0.02	0.11	**0.14**	0.04	24.6	0.26	0.00
	0.01	**0.16**	**0.12**	0.07	**0.13**	**0.10**			
	0.00	0.05	**0.12**	0.05	0.09	**0.11**			
	0.01	0.00	0.00	0.03	0.01	0.00			
3	0.12	0.01	0.00	0.12	0.03	0.00	22.4	0.33	0.01
	0.24	**0.16**	0.03	**0.19**	**0.12**	0.05			
	0.08	**0.19**	**0.15**	0.13	**0.17**	**0.13**			
	0.00	0.00	0.00	0.02	0.00	0.00			
4	0.01	0.00	0.00	0.05	0.01	0.00	14.5	0.52	0.24
	0.04	0.00	0.00	0.13	0.03	0.00			
	0.68	0.03	0.00	0.59	0.12	0.04			
	0.13	0.05	0.00	**0.11**	0.05	0.00			
5	0.12	**0.16**	0.01	0.12	**0.11**	0.02	23.4	0.28	0.01
	0.02	**0.20**	0.03	0.09	**0.14**	0.04			
	0.03	**0.15**	0.08	0.08	**0.14**	0.09			
	0.05	0.00	0.00	0.07	0.02	0.00			
6	**0.21**	0.06	0.00	**0.16**	0.08	0.01	24.3	0.30	0.00
	0.06	**0.28**	0.08	0.10	**0.18**	0.08			
	0.00	0.06	**0.19**	0.06	0.11	**0.15**			
	0.09	0.02	0.00	0.09	0.05	0.00			
7	0.02	0.22	0.00	0.08	0.17	0.01	24.3	0.29	0.00
	0.00	**0.49**	0.02	0.05	**0.25**	0.04			
	0.00	0.08	0.05	0.04	0.12	0.10			

Example with large number of orderings

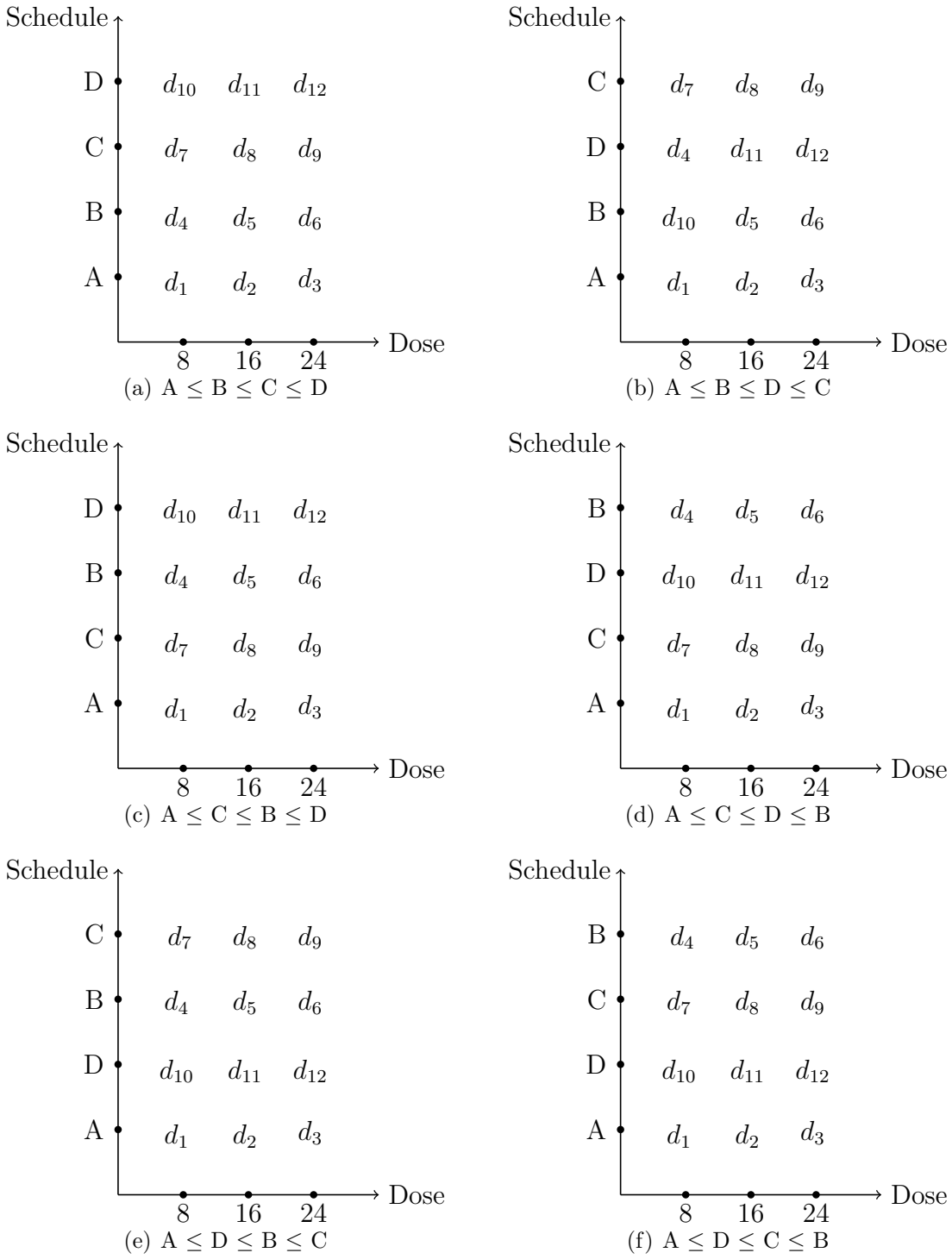
In this example, suppose we assume that Schedule A is the least toxic schedule, but that we know nothing of the toxicity relationship between Schedules B, C, and D. With this partial ordering, there are six possible arrangements for Schedule B, C and D. It could be that (1) A $\leq$ B $\leq$ C $\leq$ D. (2) A $\leq$ B $\leq$ D $\leq$ C, (3) A $\leq$ C $\leq$ B $\leq$ D, (4) A $\leq$ C $\leq$ D $\leq$ B, (5) A $\leq$ D $\leq$ B $\leq$ C or (6) A $\leq$ D $\leq$ C $\leq$ B in terms of the ordering relationship between DLT probabilities. In Figure 1, these six possible arrangements are graphically displayed, with each sub-figure representing a monotonically increasing toxicity ordering across rows (between doses) and up columns (between schedules). Within each of these six ordering possibilities for the schedules, we have a complete ordering between doses and schedules as described in the Section 2.1 of the article. Therefore, we can choose a reasonable subset of orderings for each schedule ordering possibility as described in the article and combine them into one subset of possible orderings. If we rely on the six orderings selected across rows, up columns, and up/down diagonals, then we would have a total of 36 orderings contained in the subset. The first six for Figure 1(a), are $m = 1, \ldots, m = 6$ above and the remaining 30, for Figure 1(b)–(f), could be chosen in a similar fashion. Once we have chosen the subset of possible orderings with which to work, the methods of the following section can be implemented in order to find a schedule-dose combination with an acceptable rate of toxicity.

We evaluated the performance of the proposed method using 36 orderings in Scenarios 1–3 and 5–7 of Table 2 in the article. We did not repeat Scenario 4, in which all combinations were overly toxic. Table 2 below provides summary statistics for the performance of the "partial order schedules, stopping rule" application of the design. It reports the probability that the method selects an "acceptable" combination. These combinations were defined with respect to having true DLT probabilities within $\pm 10\%$ of the target rate and are indicated in bold-face type in Table 2. Table 2 also gives the mean sample size after 1000 runs (for trials not stopped after the first two patients), the percent of overall toxicity induced and the percent of trials stopped early for safety based on the stopping rules described in the article, using $n_t = 9$. Simulations were carried out using `R` statistical package and user-friendly `R`-code for implementing the proposed design can be downloaded at `http://faculty.virginia.edu/model-based_dose-finding/`.

Table 2: *Summary statistics for "partial order schedules, stopping rule" application of the proposed method using a subset of 36 orderings for Scenarios 1–3, 5–7. Acceptable combination is defined as any combination within ± 10% of the target.*

	Scenario					
	1	2	3	5	6	7
Probability of selecting an acceptable combination as MTD	0.59	0.70	0.69	0.62	0.56	0.40
Probability of selecting no combination	0.00	0.00	0.01	0.01	0.00	0.00
Mean number of patients enrolled	26.2	27.2	24.8	25.6	26.9	28.5
Observed incidence of toxicity	0.18	0.29	0.37	0.30	0.33	0.31

Figure 1: *Possible arrangements of toxicity orderings between schedules. Toxicity increases as we move across rows and up columns of each sub-figure.*



(a) A ≤ B ≤ C ≤ D

(b) A ≤ B ≤ D ≤ C

(c) A ≤ C ≤ B ≤ D

(d) A ≤ C ≤ D ≤ B

(e) A ≤ D ≤ B ≤ C

(f) A ≤ D ≤ C ≤ B