Web-based Supplementary Materials for

A comparative study of adaptive dose-finding designs
for phase I oncology trials of combination therapies

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Tables of main results

Table 1: Summary of the operating characteristics of the 5 methods in all scenarios

	Scenarios																
Method	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	**Average**
Recommendation rates for true MTD dose combinations (%)																	
YYC	44	70	26	6	59	44	33	5	39	49	72	2	30	18	37	2	**34**
CDP	62	81	25	29	80	43	46	23	53	41	92	38	51	39	34	22	**47**
BW	50	66	24	36	58	37	28	24	39	38	83	29	38	33	33	20	**40**
WCO	56	73	32	31	77	40	37	23	49	48	86	36	39	44	41	26	**46**
HHM	45	66	28	38	64	49	31	29	47	46	70	22	30	44	42	20	**42**
Recommendation rates for overdose combinations (%)																	
YYC	23	23	54	70	27	32	42	55	26	40	n/a	47	25	41	49	54	**41**
CDP	24	18	54	36	10	41	20	39	10	34	n/a	25	26	37	47	32	**30**
BW	27	24	48	37	17	39	25	41	26	39	n/a	32	28	37	43	35	**33**
WCO	24	24	55	44	13	36	29	46	20	29	n/a	36	19	32	34	34	**32**
HHM	14	23	48	36	12	22	22	32	12	19	n/a	29	15	31	24	32	**25**
Average number of patients allocated to true MTD combinations																	
YYC	8	14	6	1	12	9	5	1	6	10	10	1	6	4	8	0	**6**
CDP	14	17	5	6	17	9	11	5	12	10	24	8	11	8	8	5	**11**
BW	11	14	5	9	12	8	6	6	10	8	23	5	8	8	6	4	**9**
WCO	14	16	7	7	16	10	7	5	11	12	21	8	8	10	9	5	**10**
HHM	11	14	6	6	9	8	3	5	8	9	15	5	5	7	7	3	**8**

Table 2: Summary of the operating characteristics of the 5 methods in all scenarios

	Scenarios																
	Overall percentage of observed toxicities (%)																
YYC	22	27	25	22	24	24	24	25	18	24	20	26	22	26	24	22	**23**
CDP	31	39	36	28	32	34	31	34	25	31	27	35	31	35	31	30	**32**
BW	30	34	32	29	31	31	29	31	27	31	27	33	31	32	30	30	**30**
WCO	28	35	33	27	26	27	23	28	25	29	26	32	26	28	26	24	**28**
HHM	22	33	28	19	15	18	15	19	17	24	21	29	18	20	17	13	**20**
	Average number of patients allocated to at a dose combination above the true MTDCs																
YYC	3	6	11	11	6	5	9	10	3	9	n/a	9	4	10	9	9	**8**
CDP	10	11	18	12	7	15	9	15	4	12	n/a	12	10	14	15	12	**12**
BW	9	10	15	11	8	12	9	12	8	12	n/a	12	10	13	14	12	**11**
WCO	7	9	16	11	4	9	6	12	5	9	n/a	11	6	9	9	8	**9**
HHM	3	11	14	7	0	3	3	6	2	6	n/a	9	1	5	3	2	**5**
	Accuracy Index																
YYC	0.4	0.72	0.47	0.31	0.58	0.45	0.46	0.3	0.43	0.54	0.37	0.36	0.5	0.42	0.58	0.34	**0.45**
CDP	0.56	0.82	0.49	0.48	0.78	0.56	0.66	0.53	0.60	0.53	0.56	0.60	0.67	0.56	0.55	0.53	**0.59**
BW	0.37	0.71	0.47	0.49	0.55	0.49	0.46	0.51	0.42	0.39	0.4	0.54	0.5	0.45	0.48	0.47	**0.48**
WCO	0.46	0.76	0.58	0.5	0.74	0.53	0.6	0.51	0.55	0.59	0.47	0.64	0.61	0.57	0.58	0.53	**0.57**
HHM	0.31	0.69	0.49	0.54	0.62	0.62	0.56	0.58	0.54	0.52	0.37	0.56	0.48	0.56	0.5	0.4	**0.52**

Additional scenarios with 'imperfect' MTDC

We also compared the operating characteristics among the 5 methods under 6 scenarios with 3×3, 4×4, and 3×4 dose combination matrices with "imperfect" MTDC's, as shown in Table 3. By 'imperfect' we mean that there is no combination with DLT rate exactly equal to the target rate ϕ. In these cases, selecting combinations, as the MTDC, with DLT rates that are within a certain range would be considered acceptable. Table 3 highlights any combination with a DLT rate within 0.05 of the target and we deem them "acceptable" if chosen as the MTDC. Under each scenario, 1000 trials were simulated. The target toxicity probability is set to $\phi = 0.30$ in Scenarios 1 and 2, $\phi = 0.33$ in Scenarios 3–6. The sample size is $n = 22$ in Scenarios 1 and 2, $n = 32$ in Scenarios 3 and 4, and $n = 36$ in Scenarios 5 and 6.

For the YYC method, we assumed gamma$(2, 2)$ as the prior distribution for α and β, and gamma$(0.1, 0.1)$ as the prior distribution for γ. The values of the marginal a priori DLT rates, p_j, are set to $(0.10, 0.20, 0.30)$ for $J = 3$, and $(0.10, 0.20, 0.30, 0.40)$ for $J = 4$, respectively. The same settings are made for q_k. The fixed probability cut-offs for dose escalation and de-escalation are $c_e = 0.80$ and $c_d = 0.45$, respectively, which are also default values used by the software. For the BW method, the variance parameter σ^2 is set to 3 in order to stabilize the implementation of the R package **rjags**. The prior probability of each dose combination is shown in Table 4. For the WCO method, we chose a subset of possible dose-toxicity orders based on ordering the combinations by rows, columns, and diagonals of the drug combination matrix, as suggested by Wages and Conaway [1]. We utilized eight possible orderings in all scenarios. A uniform prior, $\tau(m)$, was placed on the orderings. The skeleton values, $p_{jk}(m)$, were generated according to the algorithm of Lee and Cheung [2] using the **getprior** function in R package **dfcrm** [3]. Specifically, for 3×3 combinations, we used **getprior(0.05,0.30,4,9)**; for 4×4 combinations, we used **getprior(0.05,0.30,7,16)**; and for 3×4 combinations, we used **getprior(0.05,0.30,6,12)**. The location of these skeleton values was adjusted to correspond to each of the six orderings using the **getwm** function in R package **pocrm**. All simulation results were carried out using the functions of **pocrm** with a cohort size of 1 in both stages. For each simulated trial, no stopping rule was specified so as to exhaust the pre-specified maximum sample sizes above. We performed the HHM method using the SAS/IML in SAS 9.3 (SAS Institute Inc., NC). The fixed intercept β_0 is set to be -3 throughout. c_1 and c_2 are commonly set to 0.05. We set $x_1 = 1, 2, 3$ and $x_2 = 1, 2, 3$ for 3×3 dose combinations, $x_1 = 1, 2, 3, 4$ and $x_2 = 1, 2, 3, 4$ for 4×4 dose combinations, and $x_1 = 1, 2, 3$ and $x_2 = 1, 2, 3, 4$ for 3×4 dose combinations, respectively.

Overall, the results in Table 5 seem to be consistent with the results in the main paper. The WCO (37.1%) and CDP (38.3%) methods again yielded the highest average recomendation rates for MTDC's around the target rate by at least 6% over the nearest compeititor (YYC; 31.5%). These gains appear to be more substantial than in the cases in which there is a "perfect" MTDC, however this is based on a small set of six scenarios.

Table 3: Six scenarios for two-agent combination trials with an "imperfect" MTDC. Combinations with true DLT probabilites within 5% of the target rate (ϕ) are considered acceptable and are indicated in bold type.

		A								Target	Sample
		1	2	3	4	1	2	3	4	Rate (ϕ)	Size
		Scenario 1				Scenario 2				0.30	22
	3	0.20	0.50	0.66		0.18	0.50	0.60			
	2	0.06	**0.33**	0.50		0.12	0.18	0.50			
	1	0.02	0.20	**0.33**		0.06	0.12	**0.33**			
		Scenario 3				Scenario 4					
	4	**0.35**	0.40	0.42	0.45	0.43	0.65	0.79	0.95	0.33	32
B	3	0.28	**0.31**	**0.35**	**0.36**	**0.35**	0.51	0.75	0.91		
	2	0.15	0.19	0.23	**0.30**	0.20	0.39	0.63	0.88		
	1	0.05	0.09	0.20	0.25	0.05	0.25	0.50	0.80		
		Scenario 5				Scenario 6					
	3	0.30	0.40	0.50	0.60	0.40	0.68	0.80	0.99	0.33	36
	2	0.05	0.15	0.25	**0.35**	0.20	**0.35**	0.50	0.70		
	1	0.01	0.10	0.15	0.20	0.01	0.10	0.20	**0.30**		

Table 4: Prior toxicity probabilities we used in the simulation studies in the BW method in additional simualtions with an 'imperfect' MTDC.

		A							
		1	2	3	4		1	2	3	4
			3×3					4×4		
	4					0.33	0.42	0.50	0.60	
	3	0.30	0.40	0.50		0.22	0.33	0.42	0.50	
	2	0.20	0.30	0.40		0.11	0.22	0.33	0.42	
	1	0.10	0.20	0.30		0.02	0.11	0.22	0.33	
B										
			3×4							
	3	0.33	0.40	0.47	0.54					
	2	0.22	0.29	0.36	0.43					
	1	0.10	0.17	0.25	0.33					

Table 5: Summary of the operating characteristics of the 5 methods in 6 scenarios containing an "imperfect" MTDC. The table reports the percentage of simulated trials that each emthod selected, as the MTDC, an acceptable combination, defined as one with true DLT rate within 0.05 of the target rate ϕ.

	Scenarios						
Method	1	2	3	4	5	6	**Avg.**
	Recommendation rates (%) for combos within 5% of ϕ						
YYC	37.2	23.0	43.0	18.1	29.6	41.1	**31.5**
CDP	47.7	29.9	49.5	24.7	29.4	47.6	**38.3**
BW	22.5	10.5	17.1	2.9	12.6	11.5	**13.8**
WCO	46.4	23.4	48.3	22.3	36.5	50.2	**37.1**
HHM	30.5	7.3	26.9	11.4	27.9	37.5	**22.4**

References

[1] Wages NA, Conaway MR. Specifications of a continual reassessment method design for phase I trials of combined drugs. *Pharmaceutical Statistics* 2013; **12**:217–224.

[2] Lee SM, Cheung YK. Model calibration in the continual reassessment method. *Clinical Trials* 2009; **6**:227–238.

[3] Wages NA, Varhegyi N. pocrm: an R-package for phase I trials of combinations of agents. *Computer Methods and Programs in Biomedicine* 2013; **112**: 211–218.