

Supplementary Materials for Dose-finding designs for cumulative toxicities using multiple constraints

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Table 1. *Transition matrices used for the simulation scenarios 1-11.*

Scenario	Dose Level														
	1			2			3			4			5		
Scenario 1	0.89	0.08	0.03	0.83	0.12	0.05	0.79	0.14	0.07	0.74	0.16	0.1	0.68	0.19	0.13
	0	0.87	0.13	0	0.85	0.15	0	0.84	0.16	0	0.82	0.18	0	0.8	0.20
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 2	0.93	0.06	0.01	0.89	0.08	0.03	0.83	0.12	0.05	0.79	0.14	0.07	0.74	0.16	0.1
	0	0.89	0.11	0	0.87	0.13	0	0.85	0.15	0	0.84	0.16	0	0.82	0.18
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 3	0.96	0.03	0.01	0.93	0.06	0.01	0.89	0.08	0.03	0.83	0.12	0.05	0.79	0.14	0.07
	0	0.96	0.04	0	0.89	0.11	0	0.87	0.13	0	0.85	0.15	0	0.84	0.16
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 4	0.98	0.02	0	0.96	0.03	0.01	0.93	0.06	0.01	0.89	0.08	0.03	0.83	0.12	0.05
	0	0.97	0.03	0	0.96	0.04	0	0.89	0.11	0	0.87	0.13	0	0.85	0.15
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 5	0.99	0.01	0	0.98	0.02	0	0.96	0.03	0.01	0.93	0.06	0.01	0.89	0.08	0.03
	0	0.98	0.02	0	0.97	0.03	0	0.96	0.04	0	0.89	0.11	0	0.87	0.13
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 6	0.97	0.02	0.01	0.94	0.05	0.01	0.92	0.06	0.02	0.89	0.06	0.065	0.83	0.09	0.08
	0	0.90	0.10	0	0.85	0.15	0	0.75	0.25	0	0.7	0.3	0	0.65	0.35
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 7	0.89	0.09	0.2	0.83	0.12	0.05	0.79	0.14	0.07	0.74	0.17	0.09	0.68	0.20	0.12
	0	0.98	0.02	0	0.96	0.04	0	0.92	0.08	0	0.89	0.11	0	0.86	0.14
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 8	0.89	0.10	0.1	0.83	0.15	0.02	0.79	0.16	0.05	0.74	0.18	0.08	0.68	0.21	0.11
	0	0.98	0.02	0	0.98	0.02	0	0.96	0.04	0	0.94	0.06	0	0.92	0.08
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 9	0.89	0.11	0	0.83	0.16	0.01	0.79	0.19	0.02	0.74	0.21	0.05	0.68	0.25	0.07
	0	0.98	0.02	0	0.98	0.02	0	0.96	0.04	0	0.96	0.04	0	0.92	0.8
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 10	0.93	0.06	0.01	0.89	0.09	0.02	0.83	0.12	0.05	0.79	0.14	0.07	0.74	0.16	0.1
	0	0.98	0.2	0	0.98	0.02	0	0.96	0.04	0	0.92	0.8	0	0.9	0.1
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Scenario 11	0.97	0.03	0.00	0.95	0.05	0	0.93	0.07	0	0.89	0.09	0.02	0.83	0.13	0.04
	0	0.99	0.01	0	0.98	0.02	0	0.98	0.02	0	0.96	0.04	0	0.93	0.07
	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1

Table 2. Operating characteristic of the TITE-CRMMC (Time to Event Continual Reassessment Method with Multiple Constraints) when the primary and secondary constraints coincide, 24 patients. L stands for Likelihood Estimation using Staged Approach. B stands for Bayesian. The true MTD based on each constraint is specified in bold.

	Dose Level					n starting		
	1	2	3	4	5	0.5q	0.25q	0.75q
Scenario 1								
Probability of Grade 2 or higher toxicity	0.50	0.67	0.76	0.84	0.90			
Probability of DLT	0.25	0.37	0.45	0.56	0.64			
TITE-CRMMC L	86	14	1	0	0	10	9	12
TITE-CRMMC L/ Poisson	86	13	1	0	0	11	9	14
TITE-CRMMC B	83	16	1	0	0			
TITE-CRMMC B/ Poisson	82	16	1	0	0			
Benchmark	91	9	0	0	0			
TITE-CRM	71	25	4	0	0			
TITE-CRM/ Poisson	70	26	4	0	0			
Scenario 2								
Probability of Grade 2 or higher toxicity	0.35	0.50	0.67	0.76	0.84			
Probability of DLT	0.13	0.25	0.37	0.45	0.56			
TITE-CRMMC L	34	52	14	1	0	10	9	12
TITE-CRMMC L/ Poisson	33	53	14	1	0	12	10	15
TITE-CRMMC B	29	54	16	1	0			
TITE-CRMMC B/ Poisson	29	55	15	1	0			
Benchmark	32	58	9	0	0			
TITE-CRM	24	50	22	4	0			
TITE-CRM/ Poisson	23	49	23	4	0			
Scenario 3								
Probability of Grade 2 or higher toxicity	0.22	0.35	0.50	0.67	0.76			
Probability of DLT	0.07	0.13	0.25	0.37	0.45			
TITE-CRMMC L	3	29	53	14	1	13	11	16
TITE-CRMMC L/ Poisson	3	31	52	14	1	14	12	18
TITE-CRMMC B	2	28	54	15	1			
TITE-CRMMC B/Poisson	2	27	55	15	0			
Benchmark	2	29	59	9	0			
TITE-CRM	2	24	49	22	3			
TITE-CRM/Poisson	2	23	50	22	3			
Scenario 4								
Probability of Grade 2 or higher toxicity	0.11	0.22	0.35	0.50	0.67			
Probability of DLT	0.01	0.07	0.13	0.25	0.37			
TITE-CRMMC L	0	2	29	52	17	16	13	19
TITE-CRMMC L/Poisson	0	3	27	54	16	17	14	20
TITE-CRMMC B	0	2	29	56	13			
TITE-CRMMC B/Poisson	0	2	29	55	14			
Benchmark	0	2	29	59	10			
TITE-CRM	0	2	24	52	22			
TITE-CRM/ Poisson	0	2	24	53	22			
Scenario 5								
Probability of Grade 2 or higher toxicity	0.06	0.11	0.22	0.35	0.50			
Probability of DLT	0	0.01	0.07	0.13	0.25			
TITE-CRMMC L	0	0	3	29	68	19	16	22
TITE-CRMMC L/ Poisson	0	0	2	28	70	20	17	23
TITE-CRMMC B	0	0	2	31	67			
TITE-CRMMC B/ Poisson	0	0	2	31	66			
Benchmark	0	0	2	29	69			
TITE-CRM	0	0	2	27	71			
TITE-CRM/Poisson	0	0	3	27	70			

Table 3. *Operating characteristic of the TITE-CRMMC (Time to Event Continual Reassessment Method with Multiple Constraints) when the limiting constraint is the probability of DLT for scenario 6 and Grade 2 or higher toxicities for scenarios 7-11, 24 patients. L stands for Likelihood Estimation using Staged Approach. B stands for Bayesian. The true MTD based on each constraint is specified in bold.*

	Dose Level					n starting		
	1	2	3	4	5	0.5q	0.25q	0.75q
Scenario 6								
Probability of Grade 2 or higher toxicity	0.17	0.31	0.39	0.50	0.67			
Probability of DLT	0.08	0.14	0.24	0.38	0.55			
TITE-CRMMC L	3	26	46	22	3	14	12	17
TITE-CRMMC L/ Poisson	4	27	45	21	3	15	12	19
TITE-CRMMC B	1	17	55	27	1			
TITE-CRMMC B/ Poisson	1	19	52	26	2			
Benchmark	3	22	52	22	1			
TITE-CRM	3	25	51	20	1			
TITE-CRM/ Poisson	3	25	50	20	1			
Scenario 7								
Probability of Grade 2 or higher toxicity	0.50	0.67	0.76	0.84	0.9			
Probability of DLT	0.11	0.25	0.37	0.46	0.56			
TITE-CRMMC L	78	21	1	0	0	11	9	13
TITE-CRMMC L/ Poisson	78	21	1	0	0	12	10	16
TITE-CRMMC B	77	22	2	0	0			
TITE-CRMMC B/Poisson	78	20	2	0	0			
Benchmark	83	16	1	0	0			
Scenario 8								
Probability of Grade 2 or higher toxicity	0.50	0.67	0.76	0.84	0.90			
Probability of DLT	0.07	0.11	0.25	0.36	0.46			
TITE-CRMMC L	77	21	2	0	0	13	10	19
TITE-CRMMC L/ Poisson	78	20	1	0	0	14	11	20
TITE-CRMMC B	76	22	2	0	0			
TITE-CRMMC B/ Poisson	76	21	2	0	0			
Benchmark	83	16	1	0	0			
Scenario 9								
Probability of Grade 2 or higher toxicity	0.50	0.67	0.76	0.84	0.90			
Probability of DLT	0.03	0.08	0.15	0.25	0.37			
TITE-CRMMC L	77	22	2	0	0	19	12	>24
TITE-CRMMC L/ Poisson	79	20	1	0	0	20	13	>24
TITE-CRMMC B	76	22	2	0	0			
TITE-CRMMC B/ Poisson	76	21	2	0	0			
Benchmark	83	16	1	0	0			
Scenario 10								
Probability of Grade 2 or higher toxicity	0.35	0.50	0.67	0.76	0.84			
Probability of DLT	0.07	0.11	0.25	0.37	0.46			
TITE-CRMMC L	26	51	22	1	0	13	10	16
TITE-CRMMC L/ Poisson	24	52	22	2	0	14	11	18
TITE-CRMMC B	24	53	21	2	0			
TITE-CRMMC B/ Poisson	24	54	20	2	0			
Benchmark	22	61	16	1	0			
Scenario 11								
Probability of Grade 2 or higher toxicity	0.17	0.26	0.35	0.50	0.67			
Probability of DLT	0	0.01	0.02	0.14	0.26			
TITE-CRMMC L	0	3	25	47	24	20	16	>24
TITE-CRMMC L/ Poisson	0	4	27	44	26	22	17	>24
TITE-CRMMC B	0	3	25	53	20			
TITE-CRMMC B/ Poisson	0	3	25	54	18			
Benchmark	0	2	20	62	15			

Table 4. Operating characteristic of the TITE-CRMMC (Time-to-Event Continual Reassessment Method with Multiple Constraints) when primary and secondary constraints coincide, 40 patients. L stands for Likelihood Estimation using Staged Approach. B stands for Bayesian. The true MTD based on each constraint is specified in bold.

	Dose Level					n starting		
	1	2	3	4	5	0.5q	0.25q	0.75q
Scenario 1								
Probability of Grade 2 and higher toxicity	0.50	0.67	0.76	0.84	0.90			
Probability of DLT	0.25	0.37	0.45	0.56	0.64			
TITE-CRMMC L	90	10	0	0	0	10	9	12
TITE-CRMMC L / Poisson	90	10	0	0	0	11	9	14
TITE-CRMMC B	89	11	0	0	0			
TITE-CRMMC B / Poisson	88	12	0	0	0			
Benchmark	95	5	0	0	0			
TITE-CRM	78	20	1	0	0			
TITE-CRM/ Poisson	76	22	2	0	0			
Scenario 2								
Probability of Grade 2 or higher toxicity	0.35	0.50	0.67	0.76	0.84			
Probability of DLT	0.13	0.25	0.37	0.45	0.56			
TITE-CRMMC L	25	66	9	0	0	10	9	12
TITE-CRMMC L/ Poisson	24	67	10	0	0	12	10	15
TITE-CRMMC B	24	66	11	0	0			
TITE-CRMMC B/ Poisson	22	68	10	0	0			
Benchmark	25	69	5	0	0			
TITE-CRM	17	62	20	1	0			
TITE-CRM/ Poisson	17	61	20	2	0			
Scenario 3								
Probability of Grade 2 or higher toxicity	0.22	0.35	0.50	0.67	0.76			
Probability of DLT	0.07	0.13	0.25	0.37	0.45			
TITE-CRMMC L	0	26	63	10	0	13	11	16
TITE-CRMMC L/ Poisson	1	26	63	10	0	14	12	18
TITE-CRMMC B	0	24	65	10	0			
TITE-CRMMC B /Poisson B	0	23	66	10	0			
Benchmark	0	25	69	5	0			
TITE-CRM	0	18	61	20	0			
TITE-CRM/ Poisson	0	18	62	19	1			
Scenario 4								
Probability of Grade 2 or higher toxicity	0.11	0.22	0.35	0.50	0.67			
Probability of DLT	0.01	0.07	0.13	0.25	0.37			
TITE-CRMMC L	0	0	23	66	11	16	13	19
TITE-CRMMC L/Poisson	0	0	23	66	11	17	14	20
TITE-CRMMC B	0	0	23	68	8			
TITE-CRMMC B/ Poisson	0	0	24	66	10			
Benchmark	0	0	25	69	5			
TITE-CRM	0	0	19	63	18			
TITE-CRM/ Poisson	0	1	18	63	18			
Scenario 5								
Probability of Grade 2 or higher toxicity	0.06	0.11	0.22	0.35	0.50			
Probability of DLT	0	0.01	0.07	0.13	0.25			
TITE-CRMMC L	0	0	1	23	76	19	16	22
TITE-CRMMC L/ Poisson	0	0	1	22	78	20	17	23
TITE-CRMMC B	0	0	0	26	74			
TITE-CRMMC B/ Poisson	0	0	0	25	75			
Benchmark	0	0	0	25	75			
TITE-CRM	0	0	0	20	79			
TITE-CRM/ Poisson	0	0	1	21	79			

Table 5. *Operating characteristic of the TITE-CRMMC (Time to Event Continual Reassessment Method with Multiple Constraints) when the limiting constraint is the probability of DLT for scenario 6 and Grade 2 or higher toxicities for scenarios 7-11, 40 patients. L stands for Likelihood Estimation using Staged Approach. B stands for Bayesian. The true MTD based on each constraint is specified in bold.*

	Dose Level					n starting		
	1	2	3	4	5	0.5q	0.25q	0.75q
Scenario 6								
Probability of Grade 2 or higher toxicity	0.17	0.31	0.39	0.50	0.67			
Probability of DLT	0.08	0.14	0.24	0.38	0.55			
TITE-CRMMC L	1	19	61	19	0	14	12	17
TITE-CRMMC L/ Poisson	1	18	62	18	0	15	12	19
TITE-CRMMC B	0	14	65	20	0			
TITE-CRMMC B/ Poisson	0	15	64	21	0			
Benchmark	1	17	65	17	0			
TITE-CRM	1	20	63	16	0			
TITE-CRM/ Poisson	1	21	61	17	0			
Scenario 7								
Probability of Grade 2 or higher toxicity	0.50	0.67	0.76	0.84	0.90			
Probability of DLT	0.11	0.25	0.37	0.46	0.56			
TITE-CRMMC L	83	17	0	0	0	11	9	13
TITE-CRMMC L/ Poisson	83	17	0	0	0	12	10	16
TITE-CRMMC B	84	15	0	0	0			
TITE-CRMMC B/ Poisson	84	16	0	0	0			
Benchmark	89	11	0	0	0			
Scenario 8								
Probability of Grade 2 or higher toxicity	0.50	0.67	0.76	0.84	0.90			
Probability of DLT	0.07	0.11	0.25	0.36	0.46			
TITE-CRMMC L	82	17	0	0	0	13	10	19
TITE-CRMMC L/ Poisson	84	16	0	0	0	14	11	20
TITE-CRMMC B	84	16	0	0	0			
TITE-CRMMC B/ Poisson	84	16	0	0	0			
Benchmark	89	11	0	0	0			
Scenario 9								
Probability of Grade 2 or higher toxicity	0.50	0.67	0.76	0.84	0.90			
Probability of DLT	0.03	0.08	0.15	0.25	0.37			
TITE-CRMMC L	83	17	0	0	0	19	12	35
TITE-CRMMC L/ Poisson	83	16	0	0	0	20	13	38
TITE-CRMMC B	84	16	0	0	0			
TITE-CRMMC B/ Poisson	84	16	0	0	0			
Benchmark	89	11	0	0	0			
Scenario 10								
Probability of Grade 2 or higher toxicity	0.35	0.50	0.67	0.76	0.84			
Probability of DLT	0.07	0.11	0.25	0.37	0.46			
TITE-CRMMC L	17	66	17	0	0	13	10	16
TITE-CRMMC L/ Poisson	18	65	17	0	0	14	11	18
TITE-CRMMC B	19	64	16	0	0			
TITE-CRMMC B/ Poisson	18	65	16	0	0			
Benchmark	16	73	11	0	0			
Scenario 11								
Probability of Grade 2 or higher toxicity	0.17	0.26	0.35	0.50	0.67			
Probability of DLT	0	0.01	0.02	0.14	0.26			
TITE-CRMMC L	0	0	19	66	14	20	16	28
TITE-CRMMC L/ Poisson	0	1	19	66	14	22	17	30
TITE-CRMMC B	0	1	19	66	14			
TITE-CRMMC B/ Poisson	0	1	21	64	14			
Benchmark	0	0	16	73	11			