Web-based Supplementary Materials for

"Optimizing the Concentration and Bolus of a Drug Delivered by Continuous Infusion"

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Supplementary Table 1. Scenario that is the same as the elicited prior.

Scenario 1	(Same as the elicited prior)				
		Concentration			
Bolus		$c = 0.2$	$c = 0.3$	$c = 0.4$	$c = 0.5$
$q = 0.1$	$F_E(0, c, q)$	.10	.15	.15	.25
	$F_E(\frac{1}{2}, c, q)$	.25	.30	.45	.60
	$F_E(1, c, q)$	.35	.45	.60	.70
	$\pi_T(0, c, q)$	.02	.03	.03	.03
	$\pi_T(1, c, q)$	.04	.06	.08	.12
	$u^{true}(c, q)$	46.9	51.3	59.3	64.1
$q = 0.2$	$F_E(0, c, q)$	.15	.20	.25	.30
	$F_E(\frac{1}{2}, c, q)$	.40	.45	.50	.60
	$F_E(1, c, q)$	.50	.60	.70	.80
	$\pi_T(0, c, q)$	.02	.03	.03	.03
	$\pi_T(1, c, q)$	.04	.06	.08	.12
	$u^{true}(c, q)$	56.1	60.5	65.1	70.6

Supplementary Table 2. Scenario where the highest concentration is best.

Scenario 2	(Highest concentration and bolus best)				
		Concentration			
Bolus		$c = 0.2$	$c = 0.3$	$c = 0.4$	$c = 0.5$
$q = 0.1$	$F_E(0, c, q)$	.10	.15	.20	.30
	$F_E(1, c, q)$	.40	.50	.65	.80
	$\pi_T(0, c, q)$	.01	.01	.02	.02
	$\pi_T(1, c, q)$	.03	.03	.04	.05
	$u^{true}(c, q)$	49.0	54.9	62.4	71.5
$q = 0.2$	$F_E(0, c, q)$	.15	.20	.25	.30
	$F_E(1, c, q)$	.45	.55	.70	.85
	$\pi_T(0, c, q)$	.01	.01	.02	.02
	$\pi_T(1, c, q)$	.03	.03	.04	.05
	$u^{true}(c, q)$	52.6	58.4	65.9	73.8

Supplementary Table 3. Scenario where the middle concentrations are best.

Scenario 3	(Middle concentrations best)				
		Concentration			
Bolus		$c = 0.2$	$c = 0.3$	$c = 0.4$	$c = 0.5$
$q = 0.1$	$F_E(0, c, q)$	.40	.58	.62	.64
	$F_E(1, c, q)$	.48	.68	.72	.74
	$\pi_T(0, c, q)$	.06	.08	.10	.20
	$\pi_T(1, c, q)$	.08	.10	.12	.22
	$u^{true}(c, q)$	57.3	68.9	70.1	64.0
$q = 0.2$	$F_E(0, c, q)$	.42	.60	.64	.66
	$F_E(1, c, q)$	.50	.70	.74	.76
	$\pi_T(0, c, q)$	.08	.10	.12	.22
	$\pi_T(1, c, q)$	.12	.14	.16	.26
	$u^{true}(c, q)$	57.1	68.6	69.7	63.5

Supplementary Table 4. Scenario where the lowest concentration is best.

Scenario 4 (Lowest concentration best)					
		Concentration			
Bolus		$c = 0.2$	$c = 0.3$	$c = 0.4$	$c = 0.5$
$q = 0.1$	$F_E(0, c, q)$	.13	.14	.15	.16
	$F_E(1, c, q)$	.66	.68	.70	.72
	$\pi_T(0, c, q)$	.02	.06	.15	.20
	$\pi_T(1, c, q)$	.04	.12	.30	.40
	$u^{true}(c, q)$	61.1	58.7	51.6	48.0
$q = 0.2$	$F_E(0, c, q)$	.14	.15	.16	.17
	$F_E(1, c, q)$	.67	.69	.71	.73
	$\pi_T(0, c, q)$	.06	.12	.18	.24
	$\pi_T(1, c, q)$	.12	.24	.36	.48
	$u^{true}(c, q)$	58.2	53.9	49.5	45.0

Supplementary Table 5. Scenario where all treatments are excessively toxic.

Scenario 5	(All treatments excessively toxic)				
		Concentration			
Bolus		$c = 0.2$	$c = 0.3$	$c = 0.4$	$c = 0.5$
$q = 0.1$	$F_E(0, c, q)$	.10	.15	.20	.25
	$F_E(1, c, q)$	.60	.65	.70	.75
	$\pi_T(0, c, q)$	.15	.20	.25	.30
	$\pi_T(1, c, q)$	.35	.40	.45	.50
	$u^{true}(c, q)$	44.8	45.2	45.2	45.0
$q = 0.2$	$F_E(0, c, q)$	.15	.20	.25	.30
	$F_E(1, c, q)$	.65	.70	.75	.80
	$\pi_T(0, c, q)$	.20	.25	.30	.35
	$\pi_T(1, c, q)$	.40	.45	.50	.55
	$u^{true}(c, q)$	45.2	45.2	45.0	44.3

Supplementary Table 6. Scenario where all treatments have unacceptably low efficacy.

Scenario 6	(All treatments have low efficacy)				
		Concentration			
Bolus		$c = 0.2$	$c = 0.3$	$c = 0.4$	$c = 0.5$
$q = 0.1$	$F_E(0, c, q)$	.05	.06	.07	.08
	$F_E(1, c, q)$	.20	.25	.30	.35
	$\pi_T(0, c, q)$	.02	.03	.03	.03
	$\pi_T(1, c, q)$	.04	.06	.08	.12
	$u^{true}(c, q)$	38.2	40.0	41.9	43.3
$q = 0.2$	$F_E(0, c, q)$	.06	.07	.08	.09
	$F_E(1, c, q)$	.22	.27	.32	.37
	$\pi_T(0, c, q)$	.02	.03	.03	.03
	$\pi_T(1, c, q)$	.04	.06	.08	.12
	$u^{true}(c, q)$	39.3	41.2	43.1	44.4

Supplementary Table 7. Comparison of the summary R statistic and stopping percentage for various sample sizes using the assumed prior with the computed means and $\sigma = 9$ for the θ_j's and a highly non-informative prior with mean$\{\log(\theta_j)\} = 0$ and $\sigma = 20$ for all entries of $\boldsymbol{\theta}$.

Assumed prior

	n = 24		n = 36		n = 60		n = 240	
Scenario	R	% none	R	% none	R	% none	R	% none
1	0.78	6	0.79	6	0.81	6	0.87	8
2	0.87	2	0.89	2	0.91	2	0.98	2
3	0.75	8	0.75	9	0.76	11	0.82	22
4	0.78	10	0.82	12	0.87	14	0.91	17
5	0.71	80	0.72	91	0.67	98	—	100
6	0.81	73	0.83	83	0.87	93	—	100

Highly non-informative prior

	n = 24		n = 36		n = 60		n = 240	
Scenario	R	% none	R	% none	R	% none	R	% none
1	0.64	12	0.64	13	0.67	14	0.79	15
2	0.68	7	0.71	7	0.75	7	0.92	8
3	0.81	7	0.81	8	0.81	9	0.83	15
4	0.86	6	0.88	7	0.90	8	0.92	10
5	0.71	79	0.69	89	0.70	97	—	100
6	0.70	81	0.73	90	0.82	96	—	100

Supplementary Table 8. Comparison of the summary R statistic and stopping percentage for various cohort sizes. The prior standard deviation 9 was assumed for $\log(\alpha_j)$ and $\log(\beta_r)$ for all j and r.

	cohort = 1		cohort = 2		cohort = 3	
Scenario	R	% none	R	% none	R	% none
1	0.79	6	0.77	5	0.76	8
2	0.89	2	0.86	2	0.84	4
3	0.75	9	0.76	7	0.77	6
4	0.82	12	0.82	9	0.81	6
5	0.72	91	0.71	89	0.72	87
6	0.83	83	0.83	82	0.81	83

Supplementary Table 9. Comparison of the summary R statistic and stopping percentage for various prior standard deviations σ of $\log(\alpha_j)$ and $\log(\beta_r)$ for all j and r. The main results used $\sigma = 9$.

	$\sigma = 7$		$\sigma = 9$		$\sigma = 11$		$\sigma = 20$	
Scenario	R	% none	R	% none	R	% none	R	% none
1	0.84	4	0.79	6	0.75	8	0.68	11
2	0.94	1	0.89	2	0.85	3	0.76	5
3	0.71	11	0.75	9	0.77	9	0.79	9
4	0.79	15	0.82	12	0.84	11	0.87	8
5	0.72	91	0.72	91	0.71	90	0.69	89
6	0.86	80	0.83	83	0.81	85	0.76	89

Supplementary Table 10. Comparison of the summary R statistics and stopping percentages for various interpolation methods to obtain λ^{true} between the successive evaluation times s = 0, 0.125, ..., 0.875, 1.0. For infusion time s in $(0, 1)$, the true intermediate probabilities were interpolated as $\pi(s, c, q) = \pi(0, c, q) + \{\pi(1, c, q) - \pi(0, c, q)\}s^{\phi}$. The power $\phi = 1$ for linear interpolation, $\phi = 2$ for "below linear", and $\phi = 0.5$ for "above linear". The "S-shaped" interpolation method sets $\pi(0.5, c, q) = 0.5\{(\pi(0, c, q) + \pi(1, c, q))\}$ and interpolates with $\phi = 2$ for $s < 0.5$ and with $\phi = 0.5$ for $s > 0.5$. The main results used linear interpolation.

	Below linear		Linear		Above linear		$S - shaped$	
Scenario	R	% none	R	% none	R	% none	R	% none
1	0.84	6	0.79	6	0.75	7	0.81	6
2	0.92	2	0.89	2	0.84	3	0.90	2
3	0.74	10	0.75	9	0.75	9	0.75	10
4	0.68	15	0.82	12	0.87	9	0.76	13
5	0.58	90	0.72	91	0.84	91	0.72	92
6	0.92	81	0.83	83	0.78	83	0.86	83

Supplementary Table 11. Comparison of the summary R statistics and stopping percentages for various true effects $\beta_4^{true} = k\ E_{prior}(\beta_4)$ on π_T of failure to dissolve the clot within 120 minutes, i.e. $Y > 1$.

	$k=1$		$k=3$		$k=6$		$k=9$	
Scenario	R	% none	R	% none	R	% none	R	% none
1	0.79	6	0.79	11	0.79	25	0.81	37
2	0.89	2	0.89	5	0.89	12	0.89	25
3	0.75	9	0.75	16	0.77	28	0.79	40
4	0.82	12	0.82	20	0.82	35	0.81	51
5	0.72	91	0.56	93	0.46	96	0.53	98
6	0.83	83	0.83	84	0.84	88	0.79	93

Supplementary Table 12. Simulation results for the reduced 6-parameter model with Weibull hazard. Under each scenario, $u^{true}(c, q)$ denotes the expected utility of treating a patient with the combination (c, q). The value of the utility for the combination with the highest utility is highlighted in bold. Utilities of combinations that are too toxic or have insufficient effectiveness in the scenario have a gray background.

			c				
Scenario	*q*		0.2	0.3	0.4	0.5	% none
1	0.1	$u^{true}(c, q)$	46.9	51.5	59.2	64.4	2
Prior		% Sel (No. Pats.)	0% (1.2)	0% (0.1)	0% (0.1)	1% (0.6)	
means	0.2	$u^{true}(c, q)$	56.1	60.5	65.1	**70.6**	
		% Sel (No. Pats.)	0% (0.2)	0% (1.1)	1% (1.2)	96% (31.2)	
2	0.1	$u^{true}(c, q)$	49.0	54.9	62.4	71.5	1
Safe,		% Sel (No. Pats.)	0% (1.1)	0% (0.0)	0% (0.0)	0% (0.3)	
high c and	0.2	$u^{true}(c, q)$	52.6	58.4	65.9	**73.8**	
q=.2 best		% Sel (No. Pats.)	0% (0.1)	0% (1.0)	0% (1.0)	99% (32.1)	
3	0.1	$u^{true}(c, q)$	57.3	68.9	**70.1**	64.0	5
Safe,		% Sel (No. Pats.)	0% (1.5)	1% (0.5)	2% (0.9)	5% (2.0)	
middle c and	0.2	$u^{true}(c, q)$	57.1	68.6	69.7	63.5	
q=.1 best		% Sel (No. Pats.)	1% (0.5)	7% (2.9)	17% (4.6)	61% (21.7)	
4	0.1	$u^{true}(c, q)$	**61.1**	58.7	51.6	48.0	14
Safe,		% Sel (No. Pats.)	2% (2.2)	15% (3.0)	18% (3.5)	22% (7.5)	
low c and	0.2	$u^{true}(c, q)$	58.2	53.9	49.5	45.0	
q=.1 best		% Sel (No. Pats.)	12% (2.9)	9% (3.5)	4% (2.6)	4% (8.3)	
5	0.1	$u^{true}(c, q)$	44.8	45.2	**45.2**	45.0	69
Unsafe		% Sel (No. Pats.)	11% (4.8)	9% (2.9)	4% (2.0)	3% (3.2)	
	0.2	$u^{true}(c, q)$	45.2	45.2	45.0	44.3	
		% Sel (No. Pats.)	2% (1.6)	1% (1.6)	0% (1.3)	0% (3.6)	
6	0.1	$u^{true}(c, q)$	38.2	40.0	41.9	43.3	70
Safe,		% Sel (No. Pats.)	0% (1.4)	0% (0.0)	0% (0.1)	1% (0.7)	
no (c, q)	0.2	$u^{true}(c, q)$	39.3	41.2	43.1	**44.4**	
acceptable		% Sel (No. Pats.)	0% (0.2)	0% (1.0)	0% (1.1)	30% (16.4)	

Supplementary Table 13. Hypothetical case-by-case example of a 36 patient trial.

	Treatment		Outcomes		Posterior Mean Utility for Each (c, q)							
Patient	c	q	Y_E	Y_T	(.2,.1)	(.3,.1)	(.4,.1)	(.5,.1)	(.2,.2)	(.3,.2)	(.4,.2)	(.5,.2)
(Prior)	–	–	–	–	42.45	42.42	42.37	42.60	42.03	41.99	41.92	42.04
1	0.2	0.1	45	No	67.71	66.63	66.33	64.14	67.32	66.24	65.94	63.62
2	0.2	0.1	45	No	75.63	73.18	71.06	66.59	74.62	72.58	70.64	66.28
3	0.2	0.1	No	No	59.61	58.98	59.28	58.17	59.38	58.75	59.02	57.76
4	0.2	0.1	No	No	52.29	52.17	52.73	52.77	52.13	52.00	52.54	52.46
5	0.2	0.1	No	No	47.80	47.94	48.69	49.21	47.67	47.81	48.55	48.96
6	0.3	0.1	75	No	52.26	52.76	53.31	53.14	52.18	52.67	53.17	52.87
7	0.4	0.1	90	No	54.81	55.18	55.56	55.30	54.77	55.15	55.51	55.09
8	0.4	0.1	105	No	56.18	56.63	57.13	56.59	56.21	56.68	57.18	56.46
9	0.4	0.2	0	No	59.45	60.28	62.49	63.53	60.91	61.88	64.26	65.10
10	0.5	0.2	90	Yes	60.14	60.80	61.07	26.92	61.03	61.74	61.91	26.72
11	0.4	0.2	120	No	59.94	60.65	61.28	26.02	61.05	61.84	62.43	26.08
12	0.4	0.2	No	Yes	54.79	54.81	53.04	33.23	54.84	54.78	52.54	32.22
13	0.2	0.2	No	No	53.24	53.38	51.48	31.25	53.22	53.27	50.82	30.08
14	0.3	0.1	0	No	56.41	56.66	54.78	34.30	56.41	56.57	54.09	33.01
15	0.3	0.1	15	No	58.63	58.83	56.79	34.85	58.50	58.60	55.94	33.41
16	0.3	0.1	0	No	61.07	61.34	59.37	37.28	60.89	61.05	58.40	35.64
17	0.3	0.1	105	No	61.54	61.82	59.65	36.46	61.54	61.71	58.81	34.97
18	0.3	0.1	120	No	61.34	61.75	59.65	35.00	61.57	61.90	59.09	33.66
19	0.3	0.2	No	No	60.08	60.47	58.22	32.62	60.25	60.57	57.57	31.21
20	0.3	0.2	No	Yes	56.27	56.46	55.64	37.51	55.86	55.94	54.73	35.80
21	0.3	0.1	0	No	58.16	58.46	57.66	39.25	57.82	57.99	56.79	37.47
22	0.3	0.1	0	No	59.95	60.29	59.56	41.20	59.65	59.88	58.77	39.50
23	0.3	0.1	No	No	58.74	59.05	58.21	40.15	58.39	58.57	57.29	38.34
24	0.3	0.1	No	No	57.63	57.93	56.97	39.36	57.33	57.50	56.06	37.56

Supplementary Table 13. (continued) Hypothetical case-by-case example of a 36 patient trial.

	Treatment		Outcomes		Posterior Mean Utility for Each (c, q)							
Patient	c	q	Y_E	Y_T	(.2,.1)	(.3,.1)	(.4,.1)	(.5,.1)	(.2,.2)	(.3,.2)	(.4,.2)	(.5,.2)
25	0.3	0.1	No	No	56.54	56.88	55.92	38.89	56.23	56.43	54.98	37.12
26	0.3	0.1	30	No	57.72	58.00	56.91	38.77	57.35	57.48	55.89	36.89
27	0.3	0.1	No	Yes	55.38	55.67	55.17	36.98	55.11	55.31	54.58	35.56
28	0.3	0.1	0	No	56.87	57.23	56.79	38.24	56.67	56.95	56.26	36.82
29	0.3	0.1	No	No	55.94	56.27	55.77	38.17	55.71	55.95	55.19	36.76
30	0.3	0.1	105	No	56.41	56.78	56.31	37.48	56.21	56.49	55.76	36.03
31	0.3	0.1	90	No	56.83	57.27	56.80	36.23	56.73	57.09	56.35	34.79
32	0.3	0.1	120	No	56.84	57.35	56.95	35.57	57.04	57.50	56.84	34.38
33	0.3	0.2	30	No	57.80	58.30	57.87	35.24	57.92	58.37	57.69	33.97
34	0.3	0.2	75	No	58.25	58.79	58.38	34.00	58.51	59.02	58.37	32.80
35	0.3	0.2	105	No	58.31	58.92	58.62	32.34	58.82	59.44	58.93	31.30
36	0.3	0.2	45	No	58.75	59.46	59.20	32.42	59.41	60.13	59.65	31.45

Supplementary Table 14. Prior and posterior values for the hypothetical case-by-case example.

a. Prior and posterior means and standard deviations

Parameter	Prior Mean	Post Mean	Prior StdDev	Post StdDev
$log(\alpha_0)$	-1.04	-1.10	9.00	0.60
$log(\alpha_1)$	-1.60	-7.42	9.00	5.76
$log(\alpha_2)$	-7.25	-10.16	9.00	6.43
$log(\alpha_3)$	-4.74	-2.87	9.00	5.00
$log(\alpha_4)$	-2.85	-4.29	9.00	7.03
$log(\alpha_5)$	2.37	-1.21	9.00	6.11
$log(\beta_0)$	-6.10	-10.77	9.00	5.88
$log(\beta_1)$	-3.79	1.70	9.00	6.72
$log(\beta_2)$	-7.05	-5.03	9.00	8.16
$log(\beta_3)$	-5.42	-2.66	9.00	7.14
$log(\beta_4)$	-7.88	-4.76	9.00	5.79

b. Prior and posterior probabilities at s = 1, with standard deviations as subscripts.

	(c, q)							
	(.2,.1)	(.3,.1)	(.4,.1)	(.5,.1)	(.2,.2)	(.3,.2)	(.4,.2)	(.5,.2)
Prior								
$F_E(1, c, q, \boldsymbol{\theta})$	$.565_{.451}$	$.568_{.449}$	$.571_{.448}$	$.610_{.438}$	$.566_{.450}$	$.569_{.449}$	$.573_{.448}$	$.613_{.438}$
$\pi_T(1, c, q, \boldsymbol{\theta})$	$.522_{.449}$	$.527_{.448}$	$.533_{.448}$	$.569_{.442}$	$.528_{.449}$	$.533_{.448}$	$.539_{.447}$	$.613_{.438}$
Posterior								
$F_E(1, c, q, \boldsymbol{\theta})$	$.602_{.087}$	$.617_{.076}$	$.633_{.084}$	$.651_{.108}$	$.613_{.089}$	$.629_{.080}$	$.645_{.091}$	$.663_{.113}$
$\pi_T(1, c, q, \boldsymbol{\theta})$	$.195_{.121}$	$.202_{.116}$	$.235_{.132}$	$.708_{.349}$	$.197_{.120}$	$.205_{.114}$	$.241_{.132}$	$.726_{.342}$