Supplementary Material:

Dose Optimization with Simultaneous Pharmacokinetic Estimation in Adaptive Clinical Trials

Kabir Soeny*[1], Barbara Bogacka[2], and Byron Jones[3]

[1]*Novartis Healthcare Pvt. Ltd., Hyderabad, India*

[2]*School of Mathematical Sciences, Queen Mary University of London, UK*

[3]*Novartis Pharma AG, Basel, Switzerland*

This document contains supplementary material for our publication *Dose Optimization with Simultaneous Pharmacokinetic Estimation in Adaptive Clinical Trials* . Perusal of this document is not necessary to understand the main paper.

The document is organized as follows:

Section S1 contains additional data related to the simulation studies presented in the main paper.

Section S2 presents sensitivity analysis to evaluate the effect of change in assumptions and inputs on the performance of the methodology.

Finally, Section S3 contains the MATLAB® code that was written to run the simulation studies presented in this paper.

*Corresponding author email: kabir.soeny@novartis.com

S1 Additional Data from the Simulation Studies

	Stopping rule	K_a	K_e	V	ω_1	ω_2	ω_3	σ^2
$\hat{\bar{\boldsymbol{\Psi}}}$	SR1	0.8192	0.1580	17.0449	0.0870	0.0940	0.1165	0.1050
	SR2	0.8062	0.1628	15.3183	0.0892	0.0878	0.1117	0.1029
	SR3	0.8162	0.1593	16.2209	0.0863	0.0927	0.1159	0.1049
$\widehat{\text{Bias}}(\hat{\boldsymbol{\Psi}})$	SR1	-3.6	5.3	0.3	-13.0	-6.0	16.5	5.0 [**7.1**]
	SR2	-5.1	8.5	-9.9	-10.8	-12.2	11.7	2.9 [**8.7**]
	SR3	-4.0	6.2	-4.6	-13.7	-7.3	15.9	4.9 [**8.1**]
CV	SR1	8.4	22.8	16.3	48.8	18.4	32.1	19.0 [**23.7**]
	SR2	12.8	25.3	19.5	78.5	34.2	49.8	30.7 [**35.8**]
	SR3	8.4	22.8	16.3	48.8	18.4	32.1	19.0 [**27.7**]
		d_1^*	d_2^*	d_3^*	d_4^*	d_5^*	φ [RE]	CV of RE
$\boldsymbol{D}^*_{true}$		140	90	90	100	90	7.1561 [100%]	-
$\boldsymbol{D}^*$ (Initial)		150	70	80	70	80	9.0129 [79.3%]	-
Average	SR1	148.2	94.2	98.8	98.1	98.8	8.2488 [86.8%]	19.1
Recommended	SR2	133.2	85.5	89.9	89.1	89.9	8.6367 [82.9%]	22.7
$\boldsymbol{D}^*$	SR3	140.9	90.0	94.4	93.3	94.4	8.5600 [83.6%]	23.4
Average	SR1	100%						
percentage of	SR2	38.1%						
subjects assessed	SR3	75.2%						
	Stopping rule	Allocation	to	Near-	Optimum	Dose	Regimen	
Average	SR1	41.7%						
Percentage	SR2	29.8%						
of Cohorts	SR3	37.1%						

Table S1: Comparison of the methodology for the three stopping rules (SRs) as described in Section 3. For each case, the numbers in the bold are the average absolute percentage bias and the average CV of the parameter estimates.

Maximum Concentration	SR1	SR2	SR3	Time of Maximum Concentration	SR1	SR2	SR3
True C_{max}	6.05 mg/L			True T_{max}	26.01 h		
$\bar{C}_{max}$	5.95	6.47	6.23	$\bar{T}_{max}$	26.0	23.6	26.2
SD of $C_{max}^{(k)}$	0.90	0.88	0.96	SD $T_{max}^{(k)}$	0.83	7.2	3.9

Table S2: Distributions of $C_{max}^{(k)}$ and $T_{max}^{(k)}$, $k = 1, ..., 1000$ for the three stopping rules.

	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***
True C_{max}	6.05 mg/ L							
$\bar{C}_{max}$	6.20	6.11	6.17	6.10	5.33	6.10	5.40	6.11
SD of $\bar{C}_{max}^{(k)}$	1.31	0.40	0.69	0.20	0.95	0.38	0.66	0.20
True T_{max}	26.01 h							
$\bar{T}_{max}$	25.60	25.8	26.0	26.03	25.50	25.91	26.04	26.03
SD $\bar{T}_{max}^{(k)}$	1.31	2.20	0.05	0.05	1.90	1.67	0.05	0.05

Table S3: Distributions of $C_{max}^{(k)}$ and $T_{max}^{(k)}$, $k = 1, ..., 1000$ for the eight scenarios consisting of the pairs (S, c): (10,5), (1, 50), (10, 20), (1, 200), (10, 5), (1, 50), (10, 20) and (1, 200).

	c	S	K_a	K_e	V	ω_1	ω_2	ω_3	σ^2
$\hat{\bar{\boldsymbol{\Psi}}}$	5	10	0.8244	0.1548	16.9025	0.0825	0.0917	0.1352	0.1058
	50	1	0.8319	0.1543	16.5268	0.0894	0.0922	0.0988	0.1022
	20	10	0.8245	0.1542	16.4614	0.0883	0.0923	0.1100	0.1042
	200	1	0.8264	0.1542	16.4937	0.0900	0.0931	0.0991	0.1051
$\widehat{\text{Bias}}(\hat{\boldsymbol{\Psi}})$	5	10	-3.0	3.2	-0.6	-17.5	-8.3	35.3	5.8 [**10.5**]
	50	1	-2.1	2.9	-2.8	-10.6	-7.8	-1.3	2.2 [**4.2**]
p.c.	20	10	-3.0	2.8	-3.2	-11.7	-7.7	10.0	4.2 [**6.1**]
	200	1	-2.8	2.8	-3.0	-10.0	-6.9	-0.9	5.1 [**4.5**]
CV	5	10	8.8	6.3	21.4	67.7	26.9	55.8	25.4 [**30.3**]
	50	1	8.8	5.5	7.4	60.0	24.0	38.8	25.6 [**24.2**]
	20	10	4.4	3.4	11.3	32.0	12.9	21.2	13.2 [**14.0**]
	200	1	3.9	2.8	3.6	31.5	12.0	18.8	13.6 [**12.3**]
			d_1^*	d_2^*	d_3^*	d_4^*	d_5^*	φ [RE]	CV of RE
$\boldsymbol{D}^*_{true}$			140	90	90	100	90	7.1561 [100%]	-
$\boldsymbol{D}^*$ (Initial)			140	80	90	90	90	7.2888 [98.1%]	-
Average	5	10	143.9	91.5	95.9	95.2	95.9	9.5985 [74.6%]	27.5
Recommended	50	1	141.4	89.3	93.9	92.7	93.9	7.4282 [96.3%]	7.2
$\boldsymbol{D}^*$	20	10	140.8	89.2	93.4	92.9	93.4	7.9282 [90.2%]	14.9
	200	1	141.2	89.3	93.3	93.0	93.3	7.2168 [99.2%]	3.5
			$\bar{S}_1$			$\bar{S}_2$			$\bar{S}_3$
ACN (Percent	5	10	5 (37.5%)			4.40 (47.1%)			8.04 (39.2%)
Allocated to	50	1	1 (100%)						
Near-Optimum	20	10	10 (64.5%)			3.11 (69.1%)			6.63 (65.9%)
Dose Regimen)	200	1	1 (100%)						

Table S4: Data related to the simulation studies for the four scenarios: *1.* (5, 10), *2.* (50,1), *3.* (20, 10) and *4.* (200, 1), when the initial values of the parameters, $\boldsymbol{\Psi}_{oa}$, are very close to the true values. For each case, the numbers in the bold are the average absolute percentage bias and the average CV of the parameter estimates.

	c	S	K_a	K_e	V	ω_1	ω_2	ω_3	σ^2
$\bar{\widehat{\boldsymbol{\Psi}}}$	5	10	0.8291	0.1531	19.1731	0.0819	0.0968	0.1811	0.1046
	50	1	0.8257	0.1543	16.5247	0.0899	0.0898	0.1026	0.1010
	20	10	0.8233	0.1522	19.0746	0.0866	0.0991	0.1452	0.1040
	200	1	0.8224	0.1545	16.4081	0.0897	0.0937	0.1006	0.1032
$\widehat{\text{Bias}}(\widehat{\boldsymbol{\Psi}})$	5	10	-2.5	2.0	12.8	-18.1	-3.2	81.1	4.6 [**17.8**]
	50	1	-2.9	2.9	-2.8	-10.1	-10.2	2.6	1.0 [**4.6**]
p.c.	20	10	-3.1	1.4	12.2	-13.4	-0.9	45.2	4.0 [**11.5**]
	200	1	-3.3	3.0	-3.5	-10.3	-6.3	0.6	3.2 [**4.3**]
CV	5	10	9.1	6.3	20.2	70.3	25.1	79.0	26.7 [**33.8**]
	50	1	8.7	5.6	7.1	62.1	27.1	35.8	25.6 [**24.6**]
	20	10	4.4	3.2	12.3	34.2	12.1	25.2	13.2 [**15.0**]
	200	1	4.4	2.8	3.9	30.9	12.4	19.5	13.7 [**12.5**]
			d_1^*	d_2^*	d_3^*	d_4^*	d_5^*	φ_A	CV of RE
$\boldsymbol{D}^*_{true}$			140	90	90	100	90	7.1561 [100%]	-
$\boldsymbol{D}^*$ (Initial)			200	200	200	200	200	31.0280 [23.0%]	-
Average	5	10	160	100	110	110	110	8.1225 [88.0%]	27.9
Recommended	50	1	141.7	89.1	93.8	93.0	93.8	7.3952 [96.8%]	7.2
$\boldsymbol{D}^*$	20	10	162.5	100	102.2	106.6	107.0	8.7332 [90.6%]	15.4
	200	1	140.7	88.8	92.9	92.8	92.9	7.2254 [99.7%]	3.8
			$\bar{S}_1$			$\bar{S}_2$			$\bar{S}_3$
ACN (Percent	5	10	5 (22.6%)			5.95 (18.3%)			8.40 (20.4%)
Allocated to	50	1	1 (0%)						
Near-Optimum	20	10	10 (28.9%)			5.24 (20.7%)			7.58 (25.3%)
Dose Regimen)	200	1	1 (0%)						

Table S5: Data related to the simulation studies for the four scenarios: *5.* (5, 10), *6.* (50,1), *7.* (20, 10) and *8.* (200, 1), when the initial values of the parameters, $\boldsymbol{\Psi}_{ob}$, are far-off from the true values. For each case, the numbers in the bold are the average absolute percentage bias and the average CV of the parameter estimates.

	1	***2***	***3***	***4***	***5***	***6***
True C_{max}	6.05 mg/L					
$\bar{C}_{max}$	7.54	6.78	7.71	6.87	6.73	7.66
SD of $\bar{C}_{max}^{(k)}$	6.81	1.52	0.87	7.03	1.11	0.52
True T_{max}	26.01 h					
$\bar{T}_{max}$	25.02	25.85	26.04	25.65	26.03	26.04
SD of $\bar{T}_{max}^{(k)}$	4.7	2.05	0.11	3.0	0.06	0.09

Table S6: Distributions of $C_{max}^{(k)}$ and $T_{max}^{(k)}$, $k = 1, ..., 1000$ for the six scenarios of pairs of (c_1, c_2): *1.* (5, 45), *2.* (10, 40), *3.* (25, 25), *4.* (10, 190), *5.* (40, 160) and *6.* (100, 100).

	c_1	c_2	K_a	K_e	V	ω_1	ω_2	ω_3	σ^2
	5	45	0.8688	0.1536	15.6565	0.0897	0.0996	0.1315	0.1034
	10	40	0.8406	0.1480	15.5650	0.0881	0.1052	0.1370	0.1043
$\hat{\bar{\boldsymbol{\Psi}}}$	25	25	0.8507	0.1402	14.2366	0.0834	0.1169	0.1431	0.1036
	10	190	0.8538	0.1537	16.0727	0.0933	0.0956	0.1120	0.1038
	40	160	0.8327	0.1484	15.4728	0.0841	0.1060	0.1275	0.1047
	100	100	0.8470	0.1408	14.1543	0.0845	0.1163	0.1392	0.1053
	5	45	2.2	2.4	-7.9	-10.3	-0.4	31.5	3.4 [**8.3**]
	10	40	-1.1	-1.3	-8.4	-11.9	5.2	37.0	4.3 [**9.9**]
$\widehat{\text{Bias}}(\hat{\boldsymbol{\Psi}})$	25	25	0.1	-6.5	-16.3	-16.6	16.9	43.1	3.6 [**14.7**]
p.c.	10	190	0.4	2.4	-5.5	-6.7	-4.4	12.0	3.8 [**5.0**]
	40	160	-2.0	-1.1	-9.0	-15.9	6.0	27.5	4.7 [**9.5**]
	100	100	-0.4	-6.1	-16.7	-15.5	16.3	39.2	5.3 [**14.2**]
	5	45	88.2	11.9	38.5	76.6	33.5	72.6	25.6 [**49.5**]
	10	40	11.1	6.9	10.6	120.4	27.3	75.5	28.3 [**40.0**]
CV	25	25	11.6	7.6	13.2	70.2	27.1	42.6	26.4 [**28.4**]
	10	190	61.5	8.8	13.7	73.9	16.3	30.0	13.9 [**31.1**]
	40	160	5.1	3.4	6.2	35.4	13.7	22.8	13.9 [**14.4**]
	100	100	8.6	5.0	9.5	36.9	13.5	24.4	14.6 [**16.1**]
			d_1^*	d_2^*	d_3^*	d_4^*	d_5^*	φ_A [RE]	CV of RE
$\boldsymbol{D}^*_{true}$			140	90	90	100	90	7.1561 [100%]	-
$\boldsymbol{D}^*$ (Initial)			200	200	200	200	200	31.0280 [23.0%]	-
	5	45	131.9	82.6	87.1	86.4	87.1	8.6163 [83.1%]	49.3
Average	10	40	131.2	80.4	84.8	84.5	84.8	8.6512 [82.7%]	38.0
Recommended	25	25	117.6	69.6	74.0	73.3	74.0	11.3179 [63.2%]	11.4
$\boldsymbol{D}^*$	10	190	137.3	86.3	90.5	89.8	90.5	7.7288 [92.6%]	33.03
	40	160	130.6	80.4	85.1	84.1	85.1	8.0337 [89.1%]	7.8
	100	100	117.5	69.8	74.0	73.6	74.0	10.6745 [67.0%]	3.6
Average	5	45	12.7%						
percentage	10	40	19.8%						
of cohorts	25	25	31.6%						
allocated to	10	190	19.6%						
near-optimum	40	160	38.4%						
dose regimen	100	100	45.6%						

Table S7: Data related to the simulation studies for the six pairs of values of (c_1, c_2): *1.* (5, 45), *2.* (10, 40), *3.* (25, 25), *4.* (10, 190), *5.* (40, 160) and *6.* (100, 100) for the two-stage design presented in Section 5. For each case, the numbers in the bold are the average absolute percentage bias and the average CV of the parameter estimates.

S2 Sensitivity Analysis for the Adaptive Methodology

As mathematical modeling is an attempt to imitate the real world, there will be departures from the assumptions made during the modeling process, and the ability of the model to withstand them is what is called its robustness. In the context of our work, it is the uncertainty in the initial values of the PK parameters which is of concern since most estimation methods for non-linear mixed effects models are sensitive to the initial values. Cohort size, number of cohorts and number of PK sampling times are design variables and can be optimized. We plan to extend the algorithm for this optimization. For now, however, the procedure does not include this option and so we examine the effect of changing these numbers on the outcome in the simulation studies.

In this section, we shall explore the effects of varying some inputs on the results produced by our methodology, while keeping the other inputs unchanged. We firstly study the effect of using different cohort sizes and the number of cohorts on the performance of the algorithm.

S2.1 Sensitivity to the Initial Values

In the original simulation study, the true values of the parameters were taken to be $\mathbf{\Psi}_{true} = (.85, .15, 17, .1, .1, .1, .1)^T$ and the initial values were taken as $\mathbf{\Psi}_o = (1, .1, 20, .05, .15, .05, .15)^T$. We now examine whether the choice of the initial values has any bearing on the performance of the methodology. We consider vectors of varying deviation from the true values and also explore the performance of the method when the initial values are very close or coincide with the true parameter values contained in $\mathbf{\Psi}_{true}$. In all, we run six scenarios which have the following vectors as the initial values of the parameters:

$$\mathbf{\Psi}_{o1} = (1.14, .2, 22.8, .05, .15, .05, .15)^T, \qquad \mathbf{\Psi}_{o2} = (.56, .1, 11.2, .05, .15, .05, .15)^T,$$

$$\mathbf{\Psi}_{o3} = (1, .1, 20, .01, .01, .01, .01)^T, \qquad \mathbf{\Psi}_{o4} = (1, .1, 20, .50, .50, .50, .50)^T,$$

$$\mathbf{\Psi}_{o5} = (.9, .13, 18, .12, .12, .12, .12)^T, \qquad \mathbf{\Psi}_{o6} = \mathbf{\Psi}_{true}.$$

Through these six vectors, we want to see the effect of using vague initial values on the performance of our algorithm. The results from the simulation studies for these six scenarios are presented in Tables S8 and S9. The data corresponding to the initial values in the original study ($\mathbf{\Psi}_o$) are re-presented for making comparisons.

The values in Table S8 suggest that the choice of the initial values does not significantly affect the variability in the simulated distributions, as evidenced by the nearly same CVs of the parameters for

		K_a	K_e	V	ω_1	ω_2	ω_3	σ^2	
$\bar{\hat{\boldsymbol{\Psi}}}$	$\boldsymbol{\Psi}_o$	0.8192	0.1580	17.0449	0.0870	0.0940	0.1165	0.1050	
	$\boldsymbol{\Psi}_{o1}$	0.8273	0.1542	18.9483	0.0856	0.0977	0.1441	0.1039	
	$\boldsymbol{\Psi}_{o2}$	0.8177	0.1572	15.1813	0.0851	0.0949	0.1276	0.1045	
	$\boldsymbol{\Psi}_{o3}$	0.8175	0.1580	16.9072	0.0835	0.0945	0.1182	0.1059	
	$\boldsymbol{\Psi}_{o4}$	0.8117	0.1612	17.1278	0.0835	0.0934	0.1193	0.1066	
	$\boldsymbol{\Psi}_{o5}$	0.8248	0.1557	16.5119	0.0872	0.0948	0.1173	0.1050	
	$\boldsymbol{\Psi}_{o6}$	0.8232	0.1552	16.3992	0.0851	0.0964	0.1161	0.1052	
$\widehat{\text{Bias}}(\hat{\boldsymbol{\Psi}})$ p.c.	$\boldsymbol{\Psi}_o$	-3.6	5.3	.3	-13.0	-6.0	16.5	5.0	[**7.1**]
	$\boldsymbol{\Psi}_{o1}$	-2.7	2.8	11.5	-14.4	-2.3	44.1	3.9	[**11.7**]
	$\boldsymbol{\Psi}_{o2}$	-3.8	4.8	-10.7	-14.9	-5.1	27.6	4.5	[**10.2**]
	$\boldsymbol{\Psi}_{o3}$	-3.8	5.4	-.5	-16.5	-5.5	18.2	6.0	[**8.0**]
	$\boldsymbol{\Psi}_{o4}$	-4.5	7.5	.75	-16.5	-6.6	19.3	6.6	[**8.8**]
	$\boldsymbol{\Psi}_{o5}$	-3.0	3.8	-2.9	-12.8	-5.2	17.3	5.0	[**7.1**]
	$\boldsymbol{\Psi}_{o6}$	-3.1	3.5	-3.5	-14.9	-3.6	16.1	5.2	[**7.1**]
CV	$\boldsymbol{\Psi}_o$	7.5	22.5	16.3	45.8	17.90	29.0	19.1	[**22.6**]
	$\boldsymbol{\Psi}_{o1}$	6.5	13.5	14.8	46.2	18.4	29.2	19.4	[**21.2**]
	$\boldsymbol{\Psi}_{o2}$	7.1	19.3	16.0	47.0	18.6	28.4	19.3	[**22.2**]
	$\boldsymbol{\Psi}_{o3}$	7.5	24.1	15.9	47.7	18.9	30.9	18.1	[**23.3**]
	$\boldsymbol{\Psi}_{o4}$	9.0	35.4	17.6	50.1	19.1	29.8	18.5	[**25.6**]
	$\boldsymbol{\Psi}_{o5}$	7.2	18.0	15.9	46.4	18.8	28.1	18.5	[**21.9**]
	$\boldsymbol{\Psi}_{o6}$	6.8	12.2	15.3	46.6	17.9	28.3	18.5	[**20.8**]

Table S8: Comparison of statistics related to the seven scenarios of different vectors of initial values: $\boldsymbol{\Psi}_{oi}$, $i = 1, ..., 6$ and the original run with $\boldsymbol{\Psi}_o$. For each case, the numbers in the bold are the average absolute percentage bias and the average CV of the parameter estimates.

the different initial values.

The biases in the estimated parameters also seem to be invariant to the choice of the initial values of the variance parameters. This can be observed from the data corresponding to the initial values $\boldsymbol{\Psi}_{o3}$ and $\boldsymbol{\Psi}_{o4}$. However, for $\boldsymbol{\Psi}_{o1}$ and $\boldsymbol{\Psi}_{o2}$, the biases seem to be correlated with the corresponding initial values, especially for the parameters V and ω_3. Selection of initial values close to the true values do not seem to yield any additional significant benefit in reducing the bias and the variability. This is

		d_1^*	d_2^*	d_3^*	d_4^*	d_5^*	φ [RE]	CV of RE
	$\boldsymbol{\Psi}_o$	148.2	94.2	98.8	98.1	98.8	8.2488 [87.8%]	19.1
	$\boldsymbol{\Psi}_{o1}$	162.3	102.7	107.3	106.7	107.3	8.8752 [80.6%]	23.2
Average	$\boldsymbol{\Psi}_{o2}$	130.8	82.6	87.1	86.2	87.1	8.8920 [80.4%]	24.5
Recommended	$\boldsymbol{\Psi}_{o3}$	146.3	93.3	97.5	97.0	97.5	8.5297 [83.8%]	20.8
$\boldsymbol{D}^*$	$\boldsymbol{\Psi}_{o4}$	149.5	94.9	99.6	100.0	99.6	8.5888 [83.3%]	22.2
	$\boldsymbol{\Psi}_{o5}$	141.6	89.2	93.8	903.0	93.8	8.5151 [84.0%]	21.3
	$\boldsymbol{\Psi}_{o6}$	140.5	88.7	93.3	92.4	93.3	8.5039 [84.1%]	21.7

		T_1^*	T_2^*	T_3^*
	$\boldsymbol{\Psi}_o$	.10	6.75	48
	$\boldsymbol{\Psi}_{o1}$	.10	6.89	48
ξ_S^*	$\boldsymbol{\Psi}_{o2}$	.10	6.84	48
	$\boldsymbol{\Psi}_{o3}$	.10	6.74	48
	$\boldsymbol{\Psi}_{o4}$	.10	6.75	48
	$\boldsymbol{\Psi}_{o5}$	.10	6.72	48
	$\boldsymbol{\Psi}_{o6}$	.10	6.74	48

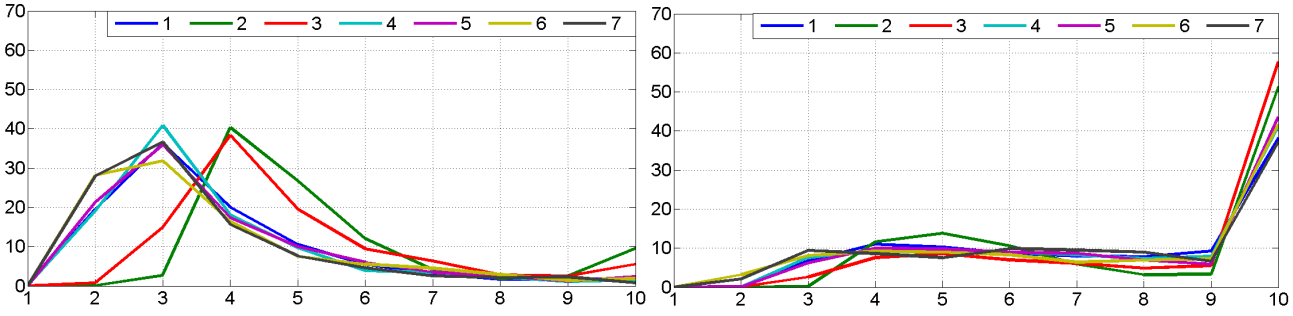
		$\bar{S}_2$	$\bar{S}_3$
	$\boldsymbol{\Psi}_o$	3.81	7.52
	$\boldsymbol{\Psi}_{o1}$	5.38	7.90
ACN	$\boldsymbol{\Psi}_{o2}$	4.97	8.31
	$\boldsymbol{\Psi}_{o3}$	3.73	7.60
	$\boldsymbol{\Psi}_{o4}$	3.83	7.65
	$\boldsymbol{\Psi}_{o5}$	3.74	7.44
	$\boldsymbol{\Psi}_{o6}$	3.56	7.35

Table S9: Comparison of statistics related to the seven scenarios of different vectors of initial values: $\boldsymbol{\Psi}_{oi}$, $i = 1, ..., 6$ and the original run with $\boldsymbol{\Psi}_o$.

evident from the insignificant difference between the data corresponding to $\boldsymbol{\Psi}_o$, $\boldsymbol{\Psi}_{o5}$ and $\boldsymbol{\Psi}_{o6}$.

An apparently counter-intuitive observation from Table S9 is the relatively higher values of the ACNs for $\boldsymbol{\Psi}_{o1}$ and $\boldsymbol{\Psi}_{o2}$ despite no significantly larger variability in the estimated parameters (as measured by the CV). To understand this anomaly, we examined the distributions for the two stopping rules for $\boldsymbol{\Psi}_{oi}$, $i = 1, ..., 6$ and compared them with the original run with $\boldsymbol{\Psi}_o$. Figure S1 presents the percentage distribution of the cohort number at which the two stopping rules SR2 and SR3 apply.

For SR2, the distributions for $\boldsymbol{\Psi}_{o1}$ and $\boldsymbol{\Psi}_{o2}$ seem to be slightly shifted to the right, as compared with the other five vectors of initial values.



(a) SR2 (b) SR3

Figure S1: Percentage distribution for the two stopping rules SR2 and SR3 for the seven scenarios consisting of choice of the initial values: $\boldsymbol{\Psi}_o$ and $\boldsymbol{\Psi}_{oi}$, $i = 1, ..., 6$.

The explanation for this behaviour can be traced to the initial dose regimen $\boldsymbol{D}_1^*$ which is administered to cohort 1 using the given initial values. For $\boldsymbol{\Psi}_o$, $\boldsymbol{D}_1^*$ for cohort 1 was found to be $(150, 70, 80, 70, 80)^T$. This is the same regimen which is administered to cohort 1 when $\boldsymbol{\Psi}_{o3}$ and $\boldsymbol{\Psi}_{o4}$ are used as initial values since the ED algorithm is not dependent on the variance parameters. However, for $\boldsymbol{\Psi}_{o1}$ and $\boldsymbol{\Psi}_{o2}$ the corresponding $\boldsymbol{D}_1^*$ are $(200, 160, 160, 160, 160)^T$ and $(110, 50, 60, 60, 60)^T$. Now, for the vector of true parameters $\boldsymbol{\Psi}_{true}$, the true dose regimen $\boldsymbol{D}_1^*$ is given as $(140, 90, 90, 100, 90)^T$. For $\boldsymbol{\Psi}_o$ (as well as for $\boldsymbol{\Psi}_{o3}$ and $\boldsymbol{\Psi}_{o4}$), since the starting dose regimen is closer to the true dose regimen, the conditions of the stopping rules are met sooner. For example, for SR2, it can be seen from the figure that in about 60% of the simulations the trial is terminated at cohort 2 or 3 for scenarios 1, 4 and 5. However, for scenarios 2 and 3, the corresponding percentages are approximately 3 and 15. Because of this, the ACNs for scenarios 2 and 3 get shifted towards the latter cohorts.

For SR3, the distributions for $\boldsymbol{\Psi}_{o1}$ and $\boldsymbol{\Psi}_{o2}$ are mostly similar except that in a higher percentage of the simulations, the trial is terminated at cohort 10. For the same reason as above, scenarios 2 and 3 have higher percentages of simulations in which the trial is stopped at the last cohort, that is, cohort 10.

The same argument can be used to explain the low ACN values for scenario 7, i.e., for the case of $\boldsymbol{\Psi}_{o6}$. Since the initial values are equal to the true parameter values, the starting dose regimen $\boldsymbol{D}_1^*$ coincides with the φ-efficient dose regimen corresponding to $\boldsymbol{\Psi}_{true}$. The proximity of $\boldsymbol{D}_1^*$ to the true dose regimen results in earlier application of the stopping rules SR2 and SR3. In fact, the ACN values for this scenario are the lowest. Furthermore, since $\boldsymbol{\Psi}_{o5}$ and $\boldsymbol{\Psi}_{o6}$ are closest to $\boldsymbol{\Psi}_{true}$, it can be seen from Figure S1 that in around 30% of the simulations, SR2 is applied at cohort 2 for these two scenarios compared to around 20% for scenarios 1, 4 and 5 and almost nil for scenarios 2 and 3. This implies that the closer the initial values are to the true values, the trial will, on average, terminate earlier.

As can be seen in Table S9, REs of the average recommended dose regimens are relatively lower for scenarios 2 and 3. Furthermore, the spread in the REs is slightly higher for these two scenarios. This means that a larger number of subjects in the simulation study are administered sub-optimal dose regimens. No significant differences are observed in the other five scenarios, though the REs for $\boldsymbol{\Psi}_{o5}$ and $\boldsymbol{\Psi}_{o6}$ are the highest.

We conclude from our analyses that while vague initial values for the variance parameters do not significantly affect the outcome, vague initial values of the PK parameters can amplify the bias and variability in the parameter estimates, lead to inefficient dose regimens and can delay the termination of the trial (evident from the higher ACNs). Initial values of the mean PK parameters should therefore be closer to the true values to minimize these departures.

S2.2 Sensitivity to the Cohort Size and the Number of Cohorts

Cohort size, c, is a design variable which is entangled with the number of cohorts, S. In the original simulation study, we took $(c, S) = (10, 10)$. Table S10 presents the data obtained by re-running the simulation study $N_{sim} = 1000$ times for different pairs of (c, S) for the stopping rule SR1. The data corresponding to the original run with (10, 10) have been inserted to facilitate comparisons. The number in bold in the percentage bias row is the average absolute percentage bias, computed by taking the average of the absolute values of the bias for the seven parameters estimates. Similarly, the bold number in the CV row is the average CV per parameter estimate.

In general, the bias and the variability in the estimated parameters decrease with increase in the cohort size and the number of cohorts. However, the percentage bias is more effectively reduced by taking a larger cohort size rather than having more cohorts. This can be inferred by noticing in Table S10 that the magnitude of the decrease in the absolute bias is larger when c is increased keeping C fixed than the other way around. For example, keeping C fixed at 10 cohorts, the average percentage biases for $c = 5$, 10 and 20 subjects are 12.1, 7.1 and 5.7. However, keeping c fixed at 10 subjects, the average percentage biases for $C = 5$, 10 and 20 subjects are 9.4, 7.1 and 7.4.

The average CV also appears to follow a similar relationship with (c, S). The dose vector administered to the last cohort, $\boldsymbol{D}^*$, tends to get closer to the true optimal dose vector as the bias decreases, which is also supported by the simulated data.

Average RE values for the seven scenarios also support the idea of preferring larger cohort sizes to having more cohorts. For fixed S, average RE increases with higher c but this is not always true when S is increased keeping c fixed.

Comparing scenarios 2 and 3, 5 and 6, it can be seen that the spread in RE is curbed by having larger cohort sizes rather than more cohorts. Furthermore, the similarity between the distributions

	c	S	K_a	K_e	V	ω_1	ω_2	ω_3	σ^2
	5	5	0.7920	0.1799	15.3946	0.0889	0.0875	0.1269	0.1033
	10	5	0.8098	0.1614	15.6219	0.0824	0.0918	0.1130	0.1063
	5	10	0.7945	0.1778	16.4839	0.0877	0.0932	0.1333	0.1044
$\bar{\hat{\boldsymbol{\Psi}}}$	10	10	0.8192	0.1580	17.0449	0.0870	0.0940	0.1165	0.1050
	10	20	0.8201	0.1565	16.5505	0.0876	0.0955	0.1200	0.1048
	20	10	0.8203	0.1556	16.9598	0.0879	0.0949	0.1090	0.1058
	20	20	0.8237	0.1548	16.4561	0.0888	0.0953	0.1102	0.1052
	5	5	-6.8	20.00	-9.4	-11.1	-12.5	26.9	3.3 [**10.3**]
	10	5	-4.7	7.6	-8.1	-17.6	-8.2	13.0	6.3 [**9.4**]
	5	10	-6.5	18.5	-3.0	-12.3	-6.8	33.3	4.4 [**12.1**]
$\widehat{\text{Bias}}(\widehat{\boldsymbol{\Psi}})$	10	10	-3.6	5.3	0.3	-13.0	-6.0	16.5	5.0 [**7.1**]
p.c.	10	20	-3.5	4.3	-2.6	-12.4	-4.5	20.0	4.8 [**7.4**]
	20	10	-3.5	3.8	-0.2	-12.1	-5.1	9.0	5.8 [**5.7**]
	20	20	-3.1	3.2	-3.2	-11.2	-4.7	10.2	5.2 [**5.8**]
	5	5	19.5	61.8	23.7	90.2	41.7	53.7	34.2 [**46.4**]
	10	5	9.9	22.7	14.0	67.0	26.4	39.1	25.7 [**29.2**]
	5	10	17.3	65.0	25.2	65.7	28.8	40.5	27.2 [**38.6**]
CV	10	10	7.5	22.5	16.3	45.8	17.90	29.0	19.1 [**22.6**]
	10	20	5.6	18.6	16.0	32.3	13.1	21.0	13.2 [**17.1**]
	20	10	4.3	3.3	11.6	32.3	13.4	20.7	13.5 [**14.1**]
	20	20	3.3	2.5	11.7	22.3	8.8	15.2	9.40 [**10.4**]
			d_1^*	d_2^*	d_3^*	d_4^*	d_5^*	φ [RE]	CV of RE
	5	5	136.1	86.7	91.1	90.3	91.1	8.8515 [80.8%]	27.4
	10	5	135.9	86.8	91.5	90.8	91.5	8.3637 [85.5%]	18.8
Average	5	10	146.5	93.4	97.7	97.4	97.7	9.1974 [77.5%]	28.1
Recommended	10	10	148.2	94.2	98.8	98.1	98.8	8.2488 [87.8%]	19.1
$\boldsymbol{D}^*$	10	20	143.5	90.4	95.2	94.9	95.2	8.5404 [83.7%]	20.2
	20	10	146.2	92.9	97.1	96.8	97.1	8.1357 [87.9%]	14.6
	20	20	142.1	89.4	94.0	93.6	94.0	8.1176 [88.1%]	13.6
				$\bar{S}_2$		$\bar{S}_3$			
	5	5		3.70		4.83			
	10	5		3.42		4.72			
	5	10		4.47		8.15			
ACN	10	10		3.81		7.52			
	10	20		3.88		9.50			
	20	10		3.43		6.90			
	20	20		3.35		7.49			

Table S10: Summary of the statistics related to the simulation studies for different values of the cohort size (c) and the number of cohorts (S). For each case, the numbers in the bold are the average absolute percentage bias and the average CV of the parameter estimates.

for scenarios 2 and 4, 4 and 5 and 6 and 7 shows that no significant benefit is accrued by having a larger number of cohorts without increasing the cohort size.

Thus, the data suggest that for a given number of subjects available for the adaptive trial, it may be better to divide them into fewer but larger cohorts to get the maximum information. However, a potential disadvantage of having large cohorts is that more subjects will get under- or overexposed to the drug before more credible parameters are derived from the subsequent cohorts. One possible remedy could be to start with a small cohort size and increase it during the trial.

S2.3 Dependence on the Number of PK Samples per Subject

Collecting more blood samples per subject (m) should give more information about the model parameters. We explore this conjecture by repeating the original simulation study which had $m = 3$ with three other values of m: $\{4, 5, 6\}$. The same design region of [.10, 48] h is used for finding the D-optimal sampling time points. For reasons of practicality, a minimum gap of 0.25 h is imposed between any two successive sampling time points. $N_{sim} = 1000$ simulations are performed for each of these three values and the performance metrics for the stopping rule SR1 are summarised in Table S11.

ξ_C^* is defined as the optimal sampling times computed using the parameter estimates from the last cohort, i.e., $\widehat{\mathbf{\Psi}}$. The results pertaining to the original run with $m = 3$ observations per subject are also included in the table for the purpose of making comparisons. The results suggest that in general, collection of more blood samples per subject leads to a reduction in the average absolute bias and the coefficient of variation of the parameter estimates. However, the gain in precision has to be weighed against the loss in economy with respect to the added costs and patient inconvenience. $m = 4$ seems to be a good trade-off between precision and economy.

A noteworthy point in the presented data is that the magnitude of decrease, in the average CV per parameter when $m = 4$ samples are taken instead of $m = 3$, is considerably higher than the pairs of $m = 5$ and $m = 4$ and also when comparing the outputs for $m = 6$ and $m = 5$. The explanation for this can be traced to the theory of optimal design of experiments. We compare the values of the optimised determinants of the Fisher information matrices (i.e., the objective function values) corresponding to the D-optimal designs for the four values of m and the parameters $\mathbf{\Psi}_{true}$, as shown in Table S12.

From the table, it can be seen that the percentage increase in the optimum determinant value is much higher when 4 samples are collected per subject as compared to the other two cases. Also, from Table S11, the reduction in the CV from taking 6 instead of 5 samples is considerably smaller, just like the comparatively smaller increase in the optimum value of the determinant of the corresponding FIMs.

	m	K_a	K_e	V	ω_1	ω_2	ω_3	σ^2	
	3	0.8192	0.1580	17.0449	0.0870	0.0940	0.1165	0.1050	
$\hat{\bar{\boldsymbol{\Psi}}}$	4	0.8131	0.1560	16.9007	0.0897	0.0944	0.1191	0.1014	
	5	0.8254	0.1550	17.2243	0.0892	0.0945	0.1152	0.1015	
	6	0.8352	0.1536	17.1299	0.0909	0.0973	0.1144	0.1004	
	3	-3.6	5.3	.3	-13.0	-6.0	16.5	5.0	[**7.1**]
$\widehat{\text{Bias}}(\hat{\boldsymbol{\Psi}})$	4	-4.3	4.0	-0.6	-10.3	-5.6	19.1	1.4	[**6.5**]
p.c.	5	-2.9	3.4	1.3	-10.8	-5.5	15.2	1.5	[**5.8**]
	6	-1.7	2.4	0.8	-9.0	-2.7	14.4	0.4	[**4.5**]
	3	7.5	22.5	16.3	45.8	17.90	29.0	19.1	[**22.6**]
CV	4	6.1	4.3	15.1	34.2	18.1	26.6	11.6	[**16.6**]
	5	4.9	4.2	13.9	31.7	17.7	24.0	8.8	[**15.0**]
	6	5.0	4.0	13.3	30.6	17.3	23.3	8.0	[**14.5**]
		d_1^*	d_2^*	d_3^*	d_4^*	d_5^*	φ [RE]	CV of RE	
Average	3	148.2	94.2	98.8	98.1	98.8	8.2488 [87.8%]	19.1	
Recommended	4	145.8	92.7	97.0	97.0	97.0	8.1192 [88.1%]	20.7	
$\boldsymbol{D}^*$	5	147.6	93.4	98.0	97.3	98.0	8.2192 [87.0%]	18.0	
	6	146.7	92.4	97.1	96.3	97.1	8.0965 [88.3%]	17.1	
		T_1^*	T_2^*	T_3^*	T_4^*	T_5^*	T_6^*		
	3	.10	6.75	48.00					
ξ_S^*	4	.11	0.36	6.81	48.00				
	5	.10	.35	6.28	7.35	48.00			
	6	.10	.35	5.83	6.04	47.71	48.00		
			$\bar{S}_2$		$\bar{S}_3$				
	3		3.81		7.52				
ACN	4		3.69		7.44				
	5		3.64		7.35				
	6		3.59		7.23				

Table S11: Comparison of statistics related to the simulation studies for different values of m.

The pattern exhibited by the average CVs is also reflected in the two average cohort numbers for the different values of m as presented in Table S11. This seems reasonable, in the light of the argument made in the previous section that larger variability in the simulated parameters leads to higher ACNs for stopping rules SR2 and SR3. A decrease in variability in the estimated parameters results in earlier

m	ξ^*	$\lvert\boldsymbol{M}(\boldsymbol{\Psi}_{true}, \xi^*)\rvert$	%-age increase in $\lvert\boldsymbol{M}(\boldsymbol{\Psi}_{true}, \xi^*)\rvert$
3	{.1, 6.60, 48}	2.96×10^6	-
4	{.1, .35, 6.67, 48}	2.45×10^7	727.7
5	{.1, .35, 6.51, 6.95, 48}	9.88×10^7	303.3
6	{.1, .35, 5.63, 6.95, 47.75, 48}	2.62×10^8	165.2

Table S12: The optimal sampling time points and the optimal objective function value for the different values of m. The values in the last column are the percentage increases in $\lvert\boldsymbol{M}(\boldsymbol{\Psi}_{true}, \xi^*)\rvert$ when m samples are collected instead of $m-1$, $m = 4, 5, 6$.

application of the two stopping rules which decreases their ACNs. Therefore, the ACNs for the two stopping rules decrease as m increases, although the reduction is very small.

An interesting observation can be made regarding the D-optimal sampling times ξ_C^*. As m increases, the optimal points tend to be around the points contained in ξ_C^* for $m = 3$. It seems that there are only three informative sampling time points and any new points would be close to one of these three points.

We conclude from our analyses that although taking $m = 4$ might improve the bias and the CV of the estimated parameters to some extent, there is no strong justification for selecting higher values of m than 4. However, from practical point of view, $m = 3$ could be more suitable as it may be difficult to collect blood samples within 15 minutes.

S3 MATLAB® Code

```
function master_nocov
N_SIMUL = 1000; % Number of simulations
ncohorts = 10; % Number of cohorts
rows = N_SIMUL*ncohorts;
sr_record = ones(N_SIMUL,4);
 beta_record = ones(rows,8);
    dose_reg_record  =  ones(rows,6);
    sam_time_record  = ones(rows,4);
    phi_record = ones(rows,2);
for i = 1:N_SIMUL
      [ beta_est, sam_time, dose_reg, phi,sr] = simulator(ncohorts) ;
    beta_record([1 + (i-1)*ncohorts: i*ncohorts],:) = [i*ones(ncohorts,1)
       beta_est];
    dose_reg_record([1 + (i-1)*ncohorts: i*ncohorts],:)  =     [i*ones(
       ncohorts,1) dose_reg];
    sam_time_record([1 + (i-1)*ncohorts: i*ncohorts],:)  = [i*ones(
       ncohorts,1) sam_time];
    phi_record([1 + (i-1)*ncohorts: i*ncohorts],:)  = [i*ones(ncohorts,1)
       phi];
    sr_record(i,:)  = [i sr];
    time_to_comp = toc(start);
end
 save('bigpicnocovrnd');
end
function  [ beta_est, sam_time, dose_reg, phi,sr] = simulator(ncohorts)
ndose = 5;   %%%% No. of doses
mi = 3; %%% Number of observations per subject
 N = 10;  %number of subjects per cohort
sr = ncohorts*ones(1,3);
 fid = fopen('PK_samples.m', 'w');
 srflag = zeros(1,3);
```

```
28 %%%   Prior values of the PK parameters
29 Ka = 1; Ke = .2; V = 20;omega1 = .05;omega2 = .15;omega3 = .05; sigma =
       .15;
30 % True values of the parameters
31 tr_Ka = .85;tr_Ke = .15;tr_V = 17;;tr_omega10 = .1;tr_omega20 = .1;
       tr_omega30 = .1; tr_sigma0 = .1;
32 true_params = [tr_Ka,tr_Ke,tr_V ,tr_omega10,tr_omega20,tr_omega30,
       tr_sigma0];
33 dose_reg = zeros(ncohorts,ndose);
34 phi = zeros(ncohorts,1);
35 beta_est = zeros(ncohorts,7);
36 sam_time = zeros(ncohorts,mi);
37 ctr = 0;
38 for i = 1:ncohorts
39             [no_need dose_reg(i,:)] = ED_algorithm(Ka,Ke,V,dose_reg(i,:)
                  ,0);
40              [phi(i) no_need2] = ED_algorithm(tr_Ka,tr_Ke,tr_V,dose_reg(i
                  ,:),1);
41              phi_and_dosereg = [phi dose_reg];
42              fid_tp= fopen('current_dose.m', 'w');
43              fprintf(fid_tp,'%f %f %f %f %f',dose_reg(i,:));
44              fclose(fid_tp);
45           %%% Stopping rule 2 %%
46              if i>1 && srflag(1) == 0
47                  if abs(sum(dose_reg(i,:)) - sum(dose_reg(i - 1,:)))/sum(
                       dose_reg(i - 1,:)) <= .05
48                      sr(1) = i;
49                      srflag(1) = 1;
50                  end
51              end
52         %%% Stopping rule 3 %%%
53          if i>1 && srflag(2) == 0
54                  if abs((dose_reg(i,:)) - (dose_reg(i - 1,:))) <= .05*
```

```
                    dose_reg(i - 1,:)
55                   sr(2) = i;
56                   srflag(2) = 1;
57                end
58          end
59          %%% Find D - optimal sampling time points %%%%%
60            [popedOutput,globalStructure,strRunDirectoryName]= poped(
                  input_ed_algo(dose_reg(i,:),Ka,Ke,V,omega1,omega2,omega3,
                  sigma,N));
61            sam_time(i,:) = sort(popedOutput.xt)
62            draw_samples(dose_reg(i,:),i, sam_time(i,:));
63            [Ka,Ke,V,omega1,omega2,omega3,sigma] = PK_estimates(dose_reg(i
                  ,:),Ka,Ke,V,omega1,omega2,omega3,sigma,i);
64            beta_est(i,:) = [Ka,Ke,V,omega1,omega2,omega3,sigma];
65       end
66     fclose all;
67 end
68 function [compare dose_reg] = ED_algorithm(Ka,Ke,V,fixed_dose,measure)
69 C_tgt = 5;
70 D_MAX = 200;
71 ndose = 5;
72 epsilon = .99;
73 kappa = 10;
74 D = ones(ndose,3);
75 D(:,1) = .1*D_MAX*D(:,1);
76 D(:,2) = .50*D_MAX*D(:,2);
77 D(:,3) = D_MAX*D(:,3);
78 if measure ==1
79     kappa = 0;
80     for m = 1:5
81         D(m,:) = fixed_dose(:,m);
82     end
83 end
```

```
compare = 10000;
time = 8;
history = ones(10000,5);
varphi = ones(10000,1);
x=1;
stop = 0;
while (x <10000 && stop < ndose)
stop = 0;
lim = size(D(1,:),2);
for i = 1:lim
          conc1 = @(t) abs (     fterm_big(D(1,i),Ka,Ke,V) *(exp(-Ke*t) -
             exp(-Ka*t))   - C_tgt );
          obj1(i) = quadl(conc1,0,time)   ;
end
grid2 = cartprod(D(1,:) , D(2,:) );
lim2 = size(grid2,1);
for i =1:lim2
         conc2 = @(t) abs ( fterm_big(grid2(i,1),Ka,Ke,V)*(exp(-Ke*(time +
             t)) - exp(-Ka*(time + t)) ) + fterm_big(grid2(i,2),Ka,Ke,V)*
            (exp(-Ke*t) - exp(-Ka*t))- C_tgt);
         obj2(i) = quadl(conc2,0,time);
end

grid3 = cartprod(D(1,:) , D(2,:) , D(3,:) );
lim3 = size(grid3,1);
for i =1:lim3
        conc3 = @(t) abs ( fterm_big(grid3(i,1),Ka,Ke,V)*(exp(-Ke*(2*time
           + t)) - exp(-Ka*(2*time + t))) + fterm_big(grid3(i,2),Ka,Ke,V)*
            (exp(-Ke*(time + t))- exp(-Ka*(time + t))) +  fterm_big(grid3(
            i,3),Ka,Ke,V)* (exp(-Ke*t)- exp(-Ka*t)) - C_tgt);
                 obj3(i) = quadl(conc3,0,time)   ;
end
grid4 = cartprod(D(1,:) , D(2,:) , D(3,:), D(4,:) );
```

```
lim4 = size(grid4,1);
for i =1:lim4
                    conc4 = @(t) abs ( fterm_big(grid4(i,1),Ka,Ke,V)* (exp(-
                       Ke*(3*time + t)) - exp(-Ka*(3*time + t)))+ fterm_big(
                       grid4(i,2),Ka,Ke,V)*(exp(-Ke*(2*time + t)) - exp(-Ka
                       *(2*time + t))) + fterm_big(grid4(i,3),Ka,Ke,V)*(exp(-
                       Ke*(time + t))- exp(-Ka*(time + t))) + fterm_big(grid4
                       (i,4),Ka,Ke,V)* (exp(-Ke*t) - exp(-Ka*t)) - C_tgt );
                    obj4(i) = quadl(conc4,0,time)  ;
end
grid5 = cartprod(D(1,:) , D(2,:) , D(3,:), D(4,:) , D(5,:));
lim5 = size(grid5,1);
for i =1:lim5
                    conc5 = @(t)  abs ( fterm_big(grid5(i,1),Ka,Ke,V)* (exp(-
                       Ke*(4*time + t)) - exp(-Ka*(4*time + t)))+ fterm_big(
                       grid5(i,2),Ka,Ke,V) * (exp(-Ke*(3*time + t)) - exp(-Ka
                       *(3*time + t))) + fterm_big(grid5(i,3),Ka,Ke,V) * (exp
                       (-Ke*(2*time + t)) - exp(-Ka*(2*time + t))) +
                       fterm_big(grid5(i,4),Ka,Ke,V)*(exp(-Ke*(time + t)) -
                       exp(-Ka*(time + t))) + fterm_big(grid5(i,5),Ka,Ke,V) *
                        (exp(-Ke*t) - exp(-Ka*t)) - C_tgt );
                    obj5(i) = quadl(conc5,0,time)  ;
                    j = mod(i,lim); if (j ==0)
                                        j = lim;
                                    end
                    k = mod(i,lim2); if (k ==0)
                                         k = lim2;
                                    end
                    l = mod(i,lim3); if (l ==0)
                                         l = lim3;
                                    end
                   m = mod(i,lim4);if (m ==0)
                                          m = lim4;
```

```
                                    end
                tp = [obj1(j) , obj2(k) , obj3(l) , obj4(m) , obj5(i)];
                cum = mean(tp);
                data7(i,:) = [ grid5(i,1) obj1(j)  grid5(i,2)  obj2(k)
                    grid5(i,3) obj3(l)  grid5(i,4)  obj4(m) grid5(i,5)
                    obj5(i)  cum];
end
sort_data = sortrows(data7, 11);
sort2 = sort_data(1,:);
reg = sort2(:,[1,3,5,7,9]);
history(x,:) = reg;
if x>1
    for i=1:5
        if abs(reg(i) - history(x-1,i))== 0
            stop = stop + 1;
        end;
    end;
end;
for i = 1:size(reg,2)
     if reg(i) == D(i,1)
         D(i,:) = max(0,min(D_MAX,[D(i,1)- kappa, D(i,1), D(i,1) + kappa
             ]));
     elseif reg(i) == D(i,2)
         D(i,:) = max(0,min(D_MAX,[D(i,2) - kappa,D(i,2), D(i,2) + kappa
             ]));   %%%% Discrete
     elseif reg(i) == D(i,3)
         D(i,:) = max(0,min(D_MAX,[D(i,3) - kappa, D(i,3), D(i,3)+ kappa
             ]));
     end
end
compare = sort_data(1,11);
varphi(x) = compare; x=x+1;
end
```

```
160 dose_reg = reg;
161  end
162 function  ft = fterm_big(D,Ka,Ke,V)
163 ft = ((D*Ka)/(V*(Ka - Ke)));
164 end
165 function  draw_samples(dose,cohort_id,sampling_time)
166 %%% True PK parameters %%%
167  ka = .85; ke = .15; v = 17;phi = [ka, ke, v];
168          N = 10;
169  tau = 8;
170 varcov = [   .1     0     0     ;
171               0     .1   0     ;
172               0      0    .01];
173 sigma = .05;
174 sampling_time = sampling_time';
175 n = size(sampling_time,1);
176 tot_pat = N*n;
177 phi_mat = repmat(phi,tot_pat,1);
178 sigma_sq = sqrt(sigma);
179  no_dose = size(dose,2);
180   for  i = 1:N
181    rnd = mvnrnd([0,0,0],varcov);
182     for  j=1:n
183          b_rnd((i-1)*n + j,:) = rnd;
184     end
185  end
186 sam_time = repmat(sampling_time,N,1);
187 phi_rand =  phi_mat.*exp(b_rnd);
188 sim_conc = zeros(tot_pat,1);
189  parfor  k = 1:tot_pat
190      concn = 0;
191        for  j=1:no_dose
192             tp1 =  (phi_rand(k,3)*(phi_rand(k,1) - phi_rand(k,2))) ;
```

```
193             tp2 = (dose(j)*phi_rand(k,1));
194             tp = tp2/tp1;
195             concn = concn + ((sam_time(k)>=((j-1)*tau))) * ...
196                 (tp* (exp(-phi_rand(k,2)*abs(sam_time(k)-(j-1)*tau)) -
                        ...
197                 exp(-phi_rand(k,1)*abs(sam_time(k)-(j-1)*tau))));
198 end
199 sim_conc(k) = concn * exp(normrnd(0,sigma_sq));%Proportional error model
200 %sim_conc(k) =  concn + normrnd(0,sigma);   % For additive model
201 end
202 subject = (cohort_id-1)*N + 1;
203 parfor i = 1:N
204       for j = 1:n
205           if (i ==1 && j==1)
206               continue;
207           else
208           subject = [subject (cohort_id-1)*N + i];
209           end
210       end
211   end
212   subject = subject';
213   data = [subject sam_time sim_conc];
214   fid = fopen('PK_samples.m', 'a');
215   fprintf(fid,'%d  %8.4f %8.4f\n',data(:,1:3)');
216 end
217 function [Ka, Ke, V,omega1,omega2,omega3,sigma] = PK_estimates(dose,Ka,Ke
      ,V,omega1,omega2,omega3,sigma,cohort_id)
218  phi0 = [Ka, Ke, V];
219 phi0 = log(phi0);
220  tau = 8;
221  N = 10;
222  n = 3;
223 mod_conc1 = @(phi,t)  ((dose(1)*phi(1))/(phi(3)*(phi(1) - phi(2)))) * (
```

```
    exp(-phi(2)*t) - exp(-phi(1)*t)) + (t >= tau).*(((dose(2)*phi(1))/(phi
    (3) * (phi(1) - phi(2)))) * (exp(-phi(2)*(t-tau)) - exp(-phi(1)*(t-tau
    )))) + (t>= (2*tau)).*(((dose(3)*phi(1))/(phi(3)*(phi(1) - phi(2))))
    *(exp(-phi(2)*(t-2*tau)) - exp(-phi(1)*(t-2*tau)))) + (t>=3*tau).*(((
    dose(4)*phi(1))/(phi(3)*(phi(1) -phi(2)))) *(exp(-phi(2)*(t-3*tau)) -
    exp(-phi(1)*(t-3*tau)))) + (t>=4*tau).* (((dose(5)*phi(1))/(phi(3)*(
    phi(1) - phi(2))))*(exp(-phi(2)*(t-4*tau)) - exp(-phi(1)*(t-4*tau))));
tplot = 0:0.01:80;
load PK_samples.m;
subject = PK_samples(:,1);
time = PK_samples(:,2);
conc = PK_samples(:,3);
dp = [subject conc];
P = [1 0 0;0 1 0;0 0 1];
xform = [1 1 1];
options = statset('nlmefit');
options = statset(options,'TolX',1e-8,'FunValCheck','Off');
 set(gcf,'visible','off')
[phi,PSI,stats,b] = nlmefit(time,conc,subject, [],mod_conc1,phi0, '
    REParamsSelect',[1 2 3],'CovPattern',P,'ErrorModel','exponential','
    ParamTransform',xform,'Options',options,'ApproximationType','LME')
   set(0,'DefaultFigureVisible','off');
  Ka = exp(phi(1));
  Ke = exp(phi(2));
  V = exp(phi(3));
  sigma = stats.mse;
end
%%% Adapted from PopED software %%%%
 function [popedInput] = input_ed_algo(dose,Ka,Ke,V,omega1,omega2,omega3,
    sigma,Nc)
popedInput.strPopEDVersion='2.13';popedInput.ng=3;popedInput.nbpop=3;
   popedInput.nb=3;
popedInput.ndocc=0;popedInput.nx=0;popedInput.na=0;
```

```
246 popedInput.NumOcc=0;popedInput.m=1;popedInput.maxni=3;
247 popedInput.minni=3;popedInput.design.groupsize=Nc;
248 popedInput.design.maxgroupsize=Nc;popedInput.design.mingroupsize=Nc;
249 popedInput.design.maxtotgroupsize=Nc;popedInput.design.mintotgroupsize=Nc
    ;
250 popedInput.d_switch=1;popedInput.iApproximationMethod=0;
251 popedInput.iFOCENumInd=1000;popedInput.iEDCalculationType=0;
252 popedInput.bUseRandomSearch=1;popedInput.bUseStochasticGradient=1;
253 popedInput.bUseLineSearch=1;popedInput.bUseExchangeAlgorithm=0;
254 popedInput.bUseBFGSMinimizer=0;popedInput.ofv_calc_type=1;
255 popedInput.prior_fim=zeros(1,0)';popedInput.optsw=[ 0 1 0 0 0];
256 popedInput.line_opta=zeros(1,0)';popedInput.line_optx=zeros(1,0)';
257 popedInput.dSeed=-1;popedInput.design.groupsize=1;popedInput.design.
    maxgroupsize=1;
258 popedInput.design.mingroupsize=1;popedInput.design.maxtotgroupsize=0;
259 popedInput.design.mintotgroupsize=0;popedInput.design.sigma=[sigma 0;0
    .00001];
260 popedInput.design.bpop=[ 0 Ka 0; 0 Ke 0; 0 V 0];
261 popedInput.design.d=[ 0 omega1 0;0 omega2 0; 0 omega3 0];
262 popedInput.design.covd=[ 0 0 0];popedInput.design.docc=zeros(3,0)';
263 popedInput.design.covdocc=zeros(0,1)';
264 popedInput.design.ni=3;popedInput.design.xt=[ 1 20 40];
265 popedInput.design.maxxt=[ 48 48 48];popedInput.design.minxt=[ .1 .1 .1];
266 popedInput.design.x=zeros(0,1)';popedInput.design.discrete_x=cell(0,1)';
267 popedInput.design.a=zeros(0,1)';popedInput.design.maxa=zeros(0,1)';
268 popedInput.design.mina=zeros(0,1)';popedInput.design.model_switch=[ 1 1
    1];
269 popedInput.notfixed_bpop=[ 1 1 1];popedInput.notfixed_d=[ 1 1 1];
270 popedInput.notfixed_covd=[ 0 0 0];
271 popedInput.notfixed_docc=zeros(0,1)';popedInput.notfixed_covdocc=zeros
    (0,1)';
272 popedInput.notfixed_sigma=[ 1 0];popedInput.notfixed_covsigma=0;
273 popedInput.bUseGrouped_xt=0;popedInput.design.G=[ 1 2 3];
```

```
274 popedInput.bUseGrouped_a=0;popedInput.design.Ga=zeros(0,1)';
275 popedInput.bUseGrouped_x=0;popedInput.design.Gx=zeros(0,1)';
276 popedInput.ff_file='model_input_big_picture.m';
277 popedInput.fg_file='sfg.m';
278 popedInput.fError_file='expo_error_model.m';
279 popedInput.strUserDistributionFile='';
280 popedInput.strEDPenaltyFile='';
281 popedInput.strAutoCorrelationFile='';
282 popedInput.modtit='One_comp_mul_dose_ed_algo';
283 popedInput.bShowGraphs=0;popedInput.use_logfile=0;
284 popedInput.output_file='output_LS_2.txt';
285 popedInput.output_function_file='function_output';
286 popedInput.strIterationFileName='';
287 popedInput.strRunFile='';popedInput.m1_switch=0;popedInput.m2_switch=0;
288 popedInput.hle_switch=0;popedInput.gradff_switch=0;
289 popedInput.gradfg_switch=0;popedInput.bLHS=0;
290 popedInput.ourzero=1e-001;popedInput.rsit_output=100;
291 popedInput.sgit_output=100;popedInput.hm1=0.001;
292 popedInput.hlf=0.001;popedInput.hlg=0.001;
293 popedInput.hm2=0.001;popedInput.hgd=0.001;
294 popedInput.hle=0.001;popedInput.AbsTol=1e-01;
295 popedInput.RelTol=1e-01;popedInput.iDiffSolverMethod=0;
296 popedInput.bUseMemorySolver=0;popedInput.iFIMCalculationType=0;
297 popedInput.rsit=125;popedInput.sgit=75;popedInput.intrsit=100;popedInput.
      intsgit=50;
298 popedInput.maxrsnullit=100;popedInput.convergence_eps=1e-001;
299 popedInput.rslxt=4;popedInput.rsla=4;popedInput.cfaxt=0.01;
300 popedInput.cfaa=0.01;popedInput.bGreedyGroupOpt=0;popedInput.EACriteria
      =1;
301 popedInput.EAStepSize=0.01;popedInput.EANumPoints=0;
302 popedInput.EAConvergenceCriteria=1e-010;
303 popedInput.bEANoReplicates=0;popedInput.BFGSConvergenceCriteriaMinStep=1e
      -001;
```

```
304 popedInput.BFGSProjectedGradientTol=0.0001;
305 popedInput.BFGSTolerancef=0.001;popedInput.BFGSToleranceg=0.9;
306 popedInput.BFGSTolerancex=0.1;popedInput.ED_samp_size=45;
307 popedInput.ED_diff_it=30;popedInput.ED_diff_percent=10;
308 popedInput.line_search_it=10;popedInput.
      iNumSearchIterationsIfNotLineSearch=10;
309 popedInput.CriterionOptions.ds_index=[ 0 0 0 0 0 0 0];
310 popedInput.parallelSettings.iCompileOption=-1;
311 popedInput.parallelSettings.iUseParallelMethod=1;
312 popedInput.parallelSettings.strAdditionalMCCCompilerDependencies='';
313 popedInput.parallelSettings.strExecuteName='calc_fim.exe';
314 popedInput.parallelSettings.iNumProcesses=2;
315 popedInput.parallelSettings.iNumChunkDesignEvals=-2;
316 popedInput.parallelSettings.strMatFileInputPrefix='parallel_input';
317 popedInput.parallelSettings.strMatFileOutputPrefix='parallel_output';
318 popedInput.parallelSettings.strExtraRunOptions='';
319 popedInput.parallelSettings.dPollResultTime=1.000000e-001;
320 popedInput.parallelSettings.strFunctionInputName='function_input';
321 popedInput.parallelSettings.bParallelRS=0;popedInput.parallelSettings.
      bParallelSG=0;
322 popedInput.parallelSettings.bParallelLS=0;
323 popedInput.parallelSettings.bParallelMFEA=0;popedInput.user_data={};
324  end
```