Simulation Results for Phase II Clinical Trial Durations

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Abstract

This paper investigates the effect of cohort size on phase II clinical trial duration by doing a simulation study of a monitoring method of Thall and Simon. We challenge the assumptions that larger cohort sizes lead to shorter trials and that continuous monitoring is impractical.

Introduction

Trials conducted according to the Thall-Simon method typically monitor the trial using cohorts. For some cohort size $c \geq 1$, the stopping rule is evaluated after every group of c patients has been treated and their outcomes recorded. If naively implemented, this would mean that the trail would suspend accrual after every c patients and wait for all patient outcomes to become known. In practice, a look-ahead rule is used.

A look-ahead rule says not to wait on outcomes that cannot effect decisions. For example, consider a trial monitoring in cohorts of size 5. It may be that the trial should stop after the fifth patient if and only if there have been no responses. If any patient is known to have responded before the sixth patient arrives, we may treat this new patient without waiting for any other outcomes.

The special case of cohorts of size 1 is called *continuous monitoring*. It is commonly believed that continuous monitoring is impractical because using such an approach would result in trials that take too long to conduct. We will present simulation results that suggest cohort size has little effect on trial duration. Furthermore, to the extent that cohort size does effect trial duration, smaller cohort sizes may actually lead to faster trials.

Simulation background

We use the clinical trial monitoring method of Thall and Simon[1] in which the probability of response is by two beta random variables, θ_S for the standard treatment S and θ_E for the experimental treatment E. The trial stops early if $P(\theta_S + \delta > \theta_E) > \pi^*$ for fixed values of δ and π^*.

We take as our primary example a trial in which θ_S has a beta(40, 60) distribution, θ_E has a beta(0.8, 1.2) distribution, $\delta = 0.1$, and $\pi^* = 0.99$. We assume a maximum of 48 patients. We also consider other parameters, but the main points are illustrated in the context of this choice of parameters.

We assume that potential patients arrive according to a Poisson process, which implies that the time between patient arrivals is exponentially distributed. If a potential patient arrives while accrual is suspended, we assume the patient balks and does not become part of the trial.

Patient observation times are modeled by a mixture distribution. If a patient does not respond, we assume that we have to wait until the end of an observation window before we can declare the patient a non-response. But if a patient does respond, we assume the time required to observe the response is exponentially distributed. The mean of this exponential distribution is set so that 95% of responses happen within the observation window. Without loss of generality, we set the observation window to have length 1 and scale the time unit for trial duration accordingly. We focus on the case of accrual rates greater than or equal to 1. For slow accrual, it is unlikely that observations will be missing when a patient arrives and so cohort size matters less. We illustrate this in the "Variations" section of this paper.

Trial duration depends on the probability of patient response in two ways. Most importantly, the probability of response determines the probability that the trial will stop early, as well as how early it will stop. Furthermore, responses are observed more quickly than non-responses: a response may be recorded at any time during the observation window, but one must wait until the end of the window to declare a non-response.

Before presenting specific simulation results, we informally discuss what to expect.
In the extreme case of certain response, trial duration will not depend on cohort size. The trial will not stop early, and accrual will seldom pause because each look-ahead will be most likely be successful. At the other extreme, certain failure, the trial will stop regardless of cohort size. In this case, trials with smaller cohort sizes will treat fewer patients before stopping. Therefore it is plausible that in trials of highly effective or highly ineffective treatments, trial using continuous monitoring may have *shorter* duration than trials using large cohorts.

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[1] Thall, P. F. and Simon, R. Practical Bayesian guidelines for phase IIB clinical trials, *Biometrics*, **50**, 337-349 (1994)

Simulation results

First we test our claim that cohort size does not substantially effect trial duration if the experimental treatment is completely effective. We set $\delta = 0.1$ in this section. We fixed the probability of response at 1 and let the accrual rate equal 1, 2, 3, …, 10. (That is, we assumed patients arrive on average once per observation window up to 10 times per observation window.) For each accrual rate, we let the cohort size vary over all proper divisors of the maximum trial size: 1, 2, 3, 4, 6, 8, 12, 16, 24. Each combination of accrual rate and cohort size was simulated 1000 times. For each accrual rate, the average trial duration was essentially constant as a function of cohort size. In each case the standard deviation of the durations divided by the average duration was less than 0.005, essentially simulation noise. Here we present the results for the slowest and fastest accrual rates. See Table 1 in the Appendix for the full data.

Cohort size	Trial duration, accrual rate 1	Trial duration, accrual rate 10
1	48.3018	5.3687
2	48.6875	5.3614
3	48.1386	5.3386
4	48.3988	5.3668
6	48.5715	5.3319
8	48.1032	5.3589
12	48.4410	5.3517
16	48.2817	5.3210
24	48.3983	5.3498

Next we look at trial duration as a function of cohort size for completely ineffective treatments. We varied the accrual rate and cohort size as before. For each accrual rate, trial duration increases with cohort size. The rate of increase is greater for slowly accruing trials than for rapidly accruing trials. Here we give the trial duration results for accrual rates 1 and 10. See Table 2 in the Appendix for intermediate accrual rates.

Cohort size	Trial duration, accrual rate 1	Trial duration, accrual rate 10
1	8.058	1.683
2	8.062	1.697
3	8.169	1.702
4	9.932	1.887
6	8.033	1.693
8	9.920	1.910
12	14.062	2.292
16	17.776	2.721
24	26.178	3.490

Of course most treatments are neither completely effective nor completely ineffective. In order to obtain an average trial duration, we need to assign some distribution to the probability of response. While a uniform distribution may seem reasonable at first glance, it most definitely is not reasonable. Unfortunately, in many oncology trials it is highly unlikely that the probability of response is near 1. We choose for simulation the same distribution on the probability of response that is used in the monitoring rule, namely beta(0.8, 1.2). After all, θ_E supposedly reflects our prior belief concerning the distribution of the probability of response on the experimental treatment. But one could argue for a much more pessimistic distribution: the majority of experimental treatments turn out to be no more effective than the standard treatment. Choosing a more pessimistic distribution would have the effect of decreasing the trial durations due to increased stopping. Also, a more pessimistic prior would increase the relative advantage of continuous monitoring.

We now give simulation results for trial duration with response rates randomly distributed according to a beta(0.8, 1.2) distribution, varying cohort size and accrual rate. As before we examined accrual rates of 1, 2, 3, …, 10 and cohort sizes 1, 2, 3, 4, 6, 8, 12, 16, and 24. In general, trial duration varies little as a function of cohort size. For the full data, see Table 3 in the Appendix. The largest variation appears for the slowest accrual. When the accrual rate is 1, the average trial duration as a function of cohort size is given in the table below.

Cohort size	Trial duration
1	33.0954
2	32.4500
3	32.6084
4	34.3972
6	33.7382
8	33.8581
12	35.9694
16	37.1299
24	40.9021

Note that the average trial duration is essentially the same for cohorts of size 1 though 12 but increases for larger cohorts.

In general, the cohort size effects trial duration less as accrual increases. To measure this, for each accrual rate we computed the ratio of the standard deviation of the average trial durations to the average of the average trial durations.

Accrual rate	stdev / mean
1	0.078025
2	0.074052
3	0.067896
4	0.067576
5	0.050444
6	0.044418
7	0.034451
8	0.032431
9	0.032493
10	0.023801

Variations

It is possible that the results of the previous section may change if the design were such that the trial stopped less frequently. To that end, we repeat our simulations with $\delta = 0$.

As before, average clinical trial duration appears to be unaffected by cohort size if the experimental treatment is completely effective. And trial duration generally increases as cohort size increases if the experimental treatment is completely ineffective. These results hold over the range of accrual rates from 1 to 10. See Tables 4 and 5 in the Appendix.

In addition to setting $\delta = 0$, we repeated our duration simulations with a more concentrated distribution on the probability of response, namely beta(2, 3). As before, the relative variation in trial durations generally decreases as accrual rate increases and the maximum relative variation occurs with accrual rate 1. The table below gives the results for accrual rate 1. The full results are in Table 6 of the Appendix.

Cohort size	Trial duration
1	47.1292
2	47.9323
3	46.9774
4	47.0784
6	47.2218
8	47.4049
12	48.2665
16	47.4868
24	48.2227

In this case the dependence of trial duration on cohort size is even less than before.

This paper has focused on the case of relatively fast accrual, accrual rates greater than or equal to 1 relative to the observation window. We claimed earlier in the paper that cohort size little effect in slowly accruing trials because it is more likely that complete data will be available as each patient arrives. This is illustrated by the results below with accrual rate 0.25.

Cohort size	Trial duration
1	187.6
2	187.4
3	187.5
4	187.6
6	187.6
8	189.6
12	191.0
16	188.6
24	191.3

There appears to be a contradiction here. We have claimed that cohort size matters little when accrual is slow, and yet our simulations results have shown the greatest dependence on cohort size when the accrual rate is 1, the slowest rate studied in most of the simulations. The key to resolving this tension is to note that trials of ineffective treatments stop earlier with smaller cohorts. For slowly accruing trials, one seldom suspends accrual for missing observations, regardless of cohort size. But smaller cohorts can lead to shorter trials due to earlier stopping.

We also simulated two other trial designs, one in which the standard treatment is much more effective and one in which the standard treatment is much less effective, both using a maximum of 60 patients. In both cases the probability of response for the simulations follows the same distribution as the prior probability of response in the trial design.

The highly effective trial has a beta(70, 30) distribution on the probability of response on the standard treatment and a beta(1.4, 0.6) prior on the probability of response on the experimental treatment. We set $\delta = 0.05$ and $\pi^* = 0.98$.

The less effective trial has a beta(20, 80) distribution on the probability of response on the standard treatment and a beta(0.4, 1.6) prior on the probability of response on the experimental treatment. We set $\delta = 0.0$ and $\pi^* = 0.99$.

Conclusions

Contrary to common belief, cohort size does not have a large effect on trial duration, provided that a look-ahead rule is used. Furthermore, the effect that it does have may be in the opposite of the commonly assumed direction, that is, increasing cohort size may increase trial duration.

Appendix

Table 1: Simulation results for δ = 0.1 and probability of response 1.0

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	48.3018	24.4045	16.4765	12.3746	10.0396	8.4984	7.3752	6.5915	5.8607	5.3687
2	48.6875	24.4745	16.3800	12.4030	10.0924	8.4921	7.4064	6.5143	5.8771	5.3614
3	48.1386	24.4223	16.4121	12.4567	10.0592	8.5454	7.3863	6.4981	5.8668	5.3386
4	48.3988	24.2700	16.4261	12.4879	10.0386	8.4798	7.4001	6.5183	5.8578	5.3668
6	48.5715	24.3561	16.3510	12.4594	10.0920	8.5410	7.3845	6.5393	5.8779	5.3319
8	48.1032	24.3646	16.6272	12.4086	10.0025	8.5283	7.3779	6.5056	5.8757	5.3589
12	48.4410	24.4439	16.4398	12.4425	10.0832	8.5322	7.3497	6.4871	5.9312	5.3517
16	48.2817	24.4842	16.4641	12.5758	10.0714	8.5348	7.3742	6.5369	5.8730	5.3210
24	48.3983	24.2851	16.3723	12.4169	10.1149	8.4731	7.3530	6.5060	5.8203	5.3498

Table 2: Simulation results for δ = 0.1 and probability of response 0.0

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	8.0548	4.5695	3.3222	2.7675	2.3811	2.1688	1.9997	1.8761	1.7748	1.6833
2	8.0622	4.5170	3.3034	2.7307	2.4186	2.1691	2.0031	1.8736	1.7860	1.6975
3	8.1687	4.5199	3.3035	2.7329	2.4068	2.1708	2.0149	1.8845	1.7739	1.7018
4	9.9317	5.4595	4.0194	3.2528	2.7789	2.4945	2.2735	2.1252	2.0148	1.8869
6	8.0326	4.5965	3.3098	2.7063	2.3864	2.1511	1.9989	1.8834	1.7944	1.6929
8	9.9196	5.6292	3.9663	3.2349	2.7898	2.5011	2.2829	2.1336	2.0100	1.9100
12	14.0620	7.5030	5.2965	4.2809	3.5927	3.1546	2.8710	2.5891	2.4598	2.2925
16	17.7759	9.4595	6.7502	5.2373	4.3914	3.8243	3.4371	3.1377	2.8898	2.7215
24	26.1775	13.5661	9.3414	7.2443	6.0048	5.1272	4.5484	4.1392	3.7726	3.4904

Table 3: Simulation results for δ = 0.1 and response distributed at beta(0.8, 1.2)

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	33.0954	17.1178	11.5114	8.7872	7.5147	6.5543	5.8640	5.4206	4.9104	4.6353
2	32.4500	16.9470	11.6566	9.1144	8.0192	6.5368	6.0230	5.3545	4.9715	4.5887
3	32.6084	16.8951	11.8382	8.9969	7.6244	6.6358	6.0758	5.3672	4.9032	4.6225
4	34.3972	17.7761	12.0032	9.4321	7.6480	6.8246	6.1719	5.6049	5.0957	4.7171
6	33.7382	17.1041	12.0131	9.2755	7.7568	6.6615	5.9850	5.3157	5.1208	4.7486
8	33.8581	17.7182	12.6609	9.6009	7.7751	6.8318	5.9613	5.4116	5.0146	4.7362
12	35.9694	18.5634	13.2110	10.0178	8.1758	7.0500	6.0469	5.5197	5.1198	4.8520
16	37.1299	18.9996	12.9979	9.9647	8.0486	6.8460	6.1745	5.6194	5.0313	4.7240
24	40.9021	20.9792	14.0331	10.8853	8.8239	7.5075	6.5951	5.8767	5.4491	4.9432

Table 4: Simulation results for δ = 0.0 and probability of response 0.0

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	10.0604	5.5910	4.0490	3.2306	2.7836	2.4862	2.2862	2.1308	2.0034	1.9082
2	10.0171	5.4527	3.9897	3.2451	2.7989	2.4873	2.2988	2.1525	1.9946	1.8896
3	10.8855	6.0714	4.2991	3.5148	3.0299	2.6267	2.4129	2.2364	2.1051	1.9876
4	9.9445	5.5866	3.9891	3.2736	2.8117	2.5074	2.2944	2.1111	2.0107	1.8946
6	14.1413	7.5436	5.3921	4.2243	3.6308	3.1970	2.8774	2.6302	2.4296	2.3078
8	9.9330	5.5164	3.9877	3.2538	2.8080	2.5103	2.2671	2.1276	2.0090	1.9126
12	13.9257	7.5087	5.4372	4.2561	3.5535	3.1916	2.8661	2.6345	2.4511	2.2990
16	18.1283	9.5025	6.6601	5.2946	4.3945	3.8230	3.4462	3.1173	2.8846	2.7032
24	26.1959	13.5273	9.3675	7.2127	6.0690	5.1803	4.5744	4.1321	3.7596	3.5068

Table 5: Simulation results for δ = 0.0 and probability of response 1.0

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	48.3018	24.4045	16.4765	12.4001	10.0335	8.4899	7.3916	6.5954	5.8600	5.3633
2	48.6875	24.4745	16.3842	12.3961	10.0702	8.4903	7.3964	6.5019	5.8825	5.3654
3	48.1386	24.4223	16.3983	12.4581	10.0728	8.5478	7.3877	6.5012	5.8633	5.3368
4	48.3988	24.2700	16.4235	12.4826	10.0417	8.4729	7.3978	6.5159	5.8664	5.3609
6	48.5715	24.3561	16.3528	12.4515	10.0775	8.5303	7.3660	6.5282	5.8697	5.3471
8	48.1032	24.3646	16.6090	12.3865	10.0214	8.5184	7.3823	6.5067	5.8934	5.3357
12	48.4410	24.4439	16.4341	12.4449	10.0810	8.5230	7.3405	6.4855	5.9253	5.3461
16	48.2817	24.4842	16.4691	12.5687	10.0579	8.5239	7.3711	6.5376	5.8478	5.3377
24	48.3983	24.2851	16.3794	12.4087	10.1199	8.4873	7.3606	6.5056	5.8261	5.3547

Table 6: Simulation results for δ = 0 and response distributed at beta(2, 3).

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	47.1292	24.1407	16.3371	12.4334	10.2418	8.6894	7.5441	6.8278	6.1550	5.7212
2	47.9323	23.7528	16.1147	12.4519	10.1567	8.6570	7.5698	6.8195	6.2045	5.6401
3	46.9774	24.1032	16.4487	12.4602	10.1893	8.7119	7.6301	6.8024	6.1529	5.6617
4	47.0784	24.1561	16.2837	12.5428	10.2107	8.5685	7.5795	6.7522	6.1587	5.6584
6	47.2218	24.3301	16.3832	12.4406	10.2118	8.7295	7.5810	6.7293	6.1190	5.6845
8	47.4049	24.3470	16.1764	12.4492	10.1954	8.6929	7.6019	6.7764	6.1640	5.6691
12	48.2665	24.4840	16.4830	12.5599	10.1791	8.6905	7.6012	6.7652	6.1484	5.6713
16	47.4868	24.3370	16.4801	12.7032	10.3324	8.7851	7.6511	6.7722	6.1673	5.6229
24	48.2227	24.3092	16.6430	12.6088	10.2461	8.7336	7.6514	6.7966	6.1382	5.6256

Table 7: Simulation results for trial with 70% mean response on standard treatment

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	45.0772	23.1647	16.2136	12.1720	10.0356	8.8143	7.6957	7.1046	6.4696	6.1914
2	46.1256	22.7923	16.1050	12.3784	10.1428	8.6393	7.8106	7.0600	6.5916	6.1660
3	45.0911	22.8001	15.7770	12.4489	9.9589	8.6390	7.6773	7.1581	6.4340	6.0606
4	45.7206	23.5318	15.9200	12.1529	10.1798	8.8332	7.6481	6.9254	6.3215	5.9605
5	45.6226	23.0559	16.0569	12.2160	10.2429	8.7495	7.7594	6.9121	6.3124	5.8381
6	46.4250	23.6813	16.2306	12.4495	10.0858	8.8253	7.5597	7.0010	6.4005	5.7931
10	45.5514	24.3206	16.0089	12.3907	10.0994	8.4889	7.4317	6.8058	6.1893	5.7243
12	48.5634	24.4440	16.7751	12.5927	10.1288	8.6991	7.6500	6.8145	6.3288	5.8547
15	48.9949	25.2448	16.7845	13.0065	10.5496	8.8169	7.9141	6.8967	6.3934	5.7140
20	49.8296	25.2452	17.1046	12.7253	10.7714	8.9665	7.8123	6.8726	6.2936	5.8066
30	52.2917	26.6436	17.7616	13.8661	11.2736	9.2578	8.2455	7.3257	6.5531	6.0847

Table 8: Simulation results for trial with 20% mean response on standard treatment

Cohort size	Accrual rate									
	1	2	3	4	5	6	7	8	9	10
1	41.1409	21.2867	14.6594	11.3561	9.1051	7.6192	6.8232	5.9871	5.5794	5.0198
2	41.2961	20.9505	14.4198	11.0579	9.0845	7.5395	6.8207	6.3016	5.6970	5.1247
3	42.6901	21.2435	14.4047	11.3216	9.0376	7.9155	7.0447	6.1617	5.6488	5.2785
4	43.5422	22.3025	14.3898	11.6108	9.4077	8.1080	6.8656	6.2247	5.6659	5.3364
5	42.3689	21.6664	14.7824	11.2167	9.4784	8.0147	7.0087	6.2549	5.6593	5.2385
6	44.8129	23.2051	15.4359	11.9228	9.5893	8.1948	7.3580	6.3929	5.8690	5.4614
10	43.7464	23.0539	15.8129	11.9307	9.8962	8.2732	7.3273	6.5013	6.0317	5.5130
12	48.2774	24.3226	16.6480	12.9289	10.3364	8.8722	7.8259	6.8504	6.2945	5.7454
15	44.4148	22.3610	15.0459	11.4203	9.4914	8.1176	6.9760	6.2949	5.6815	5.2382
20	45.8699	23.8317	16.2094	12.3096	9.9033	8.4871	7.4932	6.6756	6.0921	5.4324
30	49.8416	25.0487	17.2177	12.9292	10.6315	9.1580	8.0948	7.0829	6.3785	5.9114