Science Journal of Clinical Medicine
2014; 3(5): 82-90
Published online September 30, 2014 (http://www.sciencepublishinggroup.com/j/sjcm)
doi: 10.11648/j.sjcm.20140305.12
ISSN: 2327-2724 (Print); ISSN: 2327-2732 (Online)

Determination of sample size for two stage sequential designs in bioequivalence studies under 2x2 crossover design

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To cite this article:
Haile Mekonnen Fenta. Determination of Sample Size for Two Stage Sequential Designs in Bioequivalence Studies under 2x2 Crossover Design. *Science Journal of Clinical Medicine.* Vol. 3, No. 5, 2014, pp. 82-90. doi: 10.11648/j.sjcm.20140305.12

Abstract: Sequential design is an adaptive design that allows for pre-mature termination of a trial due to efficacy or futility based on the interim analyses. The concept of sequential statistical methods was originally motivated by the need to obtain clinical benefits under certain economic constraints. That is for a trial for a positive results, early stopping ensures that a new drug product can exploited sooner, while negative results indicated, early stopping avoids wastage of resources. In short, the right drug at the right time for the right patient. Furthermore, the possible implication of two stage sequential design/ sample size re-estimation is to adjust the sample size based on the observed variance estimated from the first stage. The purpose of this work was to determine the minimum number of sample size required to proceed the second stage of sequential design, and the simulation is done through R ve. 3.0.3 Statistical software package. In general, from our simulation study, we can understand that, for highly variable drugs (CV ≥30), the appropriate GMR value is between (0.95, 1.05), which is also appropriate for low variable drugs to achieve the minimum sample size required to conduct any clinical trials.

Keywords: Two Stage Sequential Design, Geometric Mean Ratio, Bioequivalence Study, Power and Sample Size

1. Introduction

The sequential approach has been a natural way to proceed throughout the history of experimentation. Perhaps the earliest proponent was Noah, who on successive days released a dove from the Ark in order to test for the presence of dry land during the subsidence of the Flood [1]. Sequential design is an adaptive design this allows for pre mature termination of a trial due to efficacy or futility, based on the interim analyses. That is the right drug at the right time for the right patient. In general; Sequential methods typically lead to savings in sample-size, time, and cost when compared with the classic design with a fixed sample-size. The main purpose of sequential design is that, if the investigated active substance is known to have adverse effects, it may be necessary to use patients instead under suitable precautions and supervision. And the two drugs are said to be average bioequivalence (ABE) for second stage of sequential design,if and only if the confidence interval (1-2α)x100% for the ratio of test to reference formulation is contained within the regulatory limits of ($\theta 1, \theta 2$), specifically according to some regulatory agencies, like Food and Drug Administration's (FDA) 0.8-1.25, or -0.2231436 – 0.2231436 for both AUC and C_{max}. A principal reasoning for conducting a group sequential test is discussed in detail in [2] and its aim is simply to d*ecrease the sample size* of the study units under two stage sequential designs.

A sample size re-estimation (SSR) refers to an adaptive design that allows for sample size adjustment or re-sampling based on the review of interim analyses results. The sample size requirements for the trial are sensitive to the effect size and its variability [3]. That is inaccurate estimation of the effect size and its variability leads overpowered or underpowered results, neither of which is desirable. If a trial is underpowered, when the variance used in the power calculation is too low or the chosen effect size overly optimistic, it will not be able to detect a clinically meaningful difference, and consciously prevent a potentially effective drug from being delivered to patients. On the other hand, if the trial is overpowered, it could lead to unnecessary exposure of many patients to a potentially

harmful compound when the drug, in fact, is not effective [4].

The application of group sequential approaches to the BE studies differs from their application to most other types of clinical studies because the former generally involves crossover designs, testing of equivalence hypotheses, and testing based on t-distributions, whereas the later generally involves parallel designs with testing of difference hypotheses [5].At the i^{th} stage of a group sequential BE trial, data are analyzed from the first (n_i) of planned maximum number of subjects n, and the trial is stopped and BE is concluded if and only if the $(1-2\alpha i)\times 100\%$ CI for the test to reference ratios are entirely contained within the interval [80, 125%]for both C_{max} (maximum drug concentration) and (the area under the drug concentration verses curve [6]. AUC is often used to measure the extent of absorption or the total amount of drug absorbed in the body). Otherwise the trial continues to the second stage [7].

2. Methods

2.1. Two Stage Design

First initial group of subjects are treated and data are analyzed, then if bioequivalence are not demonstrated, an additional subject can be employed, and the results from both groups combine for final statistical analyses [7, 8]. In general, two stage group sequential design with interim look after $n_1$subject's complete and final look after $(n=n_1+n_2)$ subjects complete. Here we have the following potential decisions.

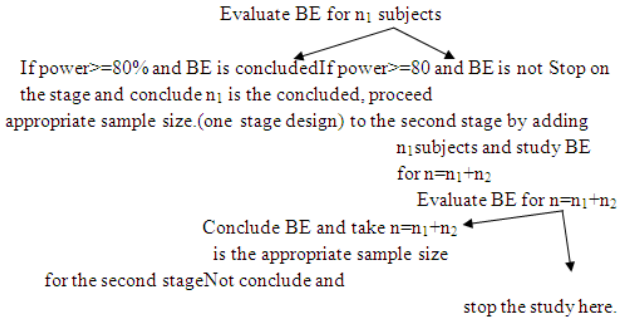

Figure 1. *two stage sequential design*

More generally, the two stagesfor this design can be summarizedas follows:

1. In stage one (for n_1 subjects),after analyzing the given data, we decide to:
   a. Stop and claim bioequivalence.
   b. Continue the trial in second stage for $(n=n_1+n_2)$ subjects.
2. In stage two (for $n=n_1+n_2$ subjects)to:
   a. Stop and claim bioequivalence.
   b. Stop and do not claim bioequivalence.

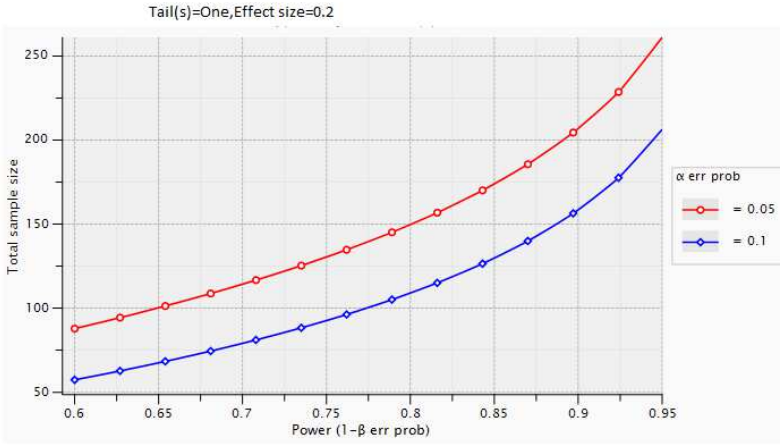

Figure 2. *The relationship between type one error, power and sample size.*

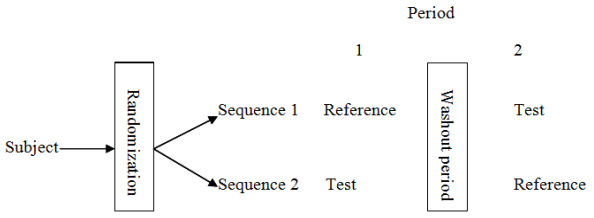

Figure 3. *The simple 2x2 crossover design*

The minimum sample size for stage two is 2 (if the decision rule determined that the study should continue to stage 2) and there is no upper limit to the size of stage 2. This can be expressed as: Sample size for stage2 is $[2, \infty)$ and here equal sample size assumption is also under consideration.

Consider a 2x2 crossover trial where we wish to compare reference (R) and test(T) using two sequences of treatment (RT and TR) given in two periods [9,10]. Let n_1 and $n_2$subjects be allocated to the two sequences, respectively. Two statistical approaches are suggested in literature for testing bioequivalence between T and R. These are:

Two One Sided Hypothesis Tests *(TOST)* procedure at α significance level and Let θ_L and θ_U are respectively lower

and upper known clinically meaningful bioequivalence limits and θbe the parameter of interest [11,12. 13].

In TOST procedure, two sided bioequivalence test is divided in to two one-sided tests in the following manner:

$$\text{Test1: } H_o^+ : \theta \le \theta L \text{ versus } H1^+ : \theta > \theta L$$

$$\text{Test1: } H_o^- : \theta L \ge \theta \text{ versus } H_1^- \theta < \theta L$$

(1-2α) x100% Confidence Interval Procedure: During the planning stage of bioavailability (BA) and bioequivalence (BE) study, the clinicians and the statisticians are able to answer the following questions [14, 15, 16, 17, and 18]. How many subjects are needed in order to achieve a desired power (commonly 80%) to establish BE between two formulations within clinically/may not be statistically important limits (±20% of the reference mean)? If only small number of subjects is available in hand due to limited resources/budget or some medical considerations, what do we have to do? In order to answer the above critical questions, a statistical approach for *sample size determination* is employed [17, 18].

2.2. Simulation Methodology and Formulas

Both lower and upper confidence intervals are simulated based on the following formulas. And the proportion of the simulated confidence interval contained within (0.8, 1.25) is computed. Let L_1 and U_1 be the lower and upper intervals, respectively.

$$L1=\frac{\overline{X}T}{\overline{X}R} - t(\alpha, n1+n2-2)\hat{\sigma}d\sqrt{\frac{1}{n1}+\frac{1}{n2}}$$

$$U1=\frac{\overline{X}T}{\overline{X}R} + t(\alpha, n1+n2-2)\hat{\sigma}d\sqrt{\frac{1}{n1}+\frac{1}{n2}}$$

Additionally, the power was calculated based on the modification of [7].

$$1-\beta=F_t\left(\frac{\ln(1.25/\theta)}{s\sqrt{2/n}} - t1-\alpha, df, df\right) - F_t\left(\frac{-\ln(1.25/\theta)}{s\sqrt{2/n}} - t1-\alpha, df, df\right)$$

where; 1-β is the power, df is the degrees of freedom associated with the error, theF_t (x, df) is the cumulative distribution functions of students' t-distribution with DF degrees of freedom, and lastly, $t_{1-\alpha}, DF$ is the (1-α)th percentile of a student's t-density function. "s" is the sample standard deviation (estimate of σ) which is calculated from ANOVA on the ln(Test/Reference)=ln(Test)-ln(Reference) differences using stage/sequence, and stage*sequence effects in the model[3]. And finally, GMR (θ) is the ratio of Test mean and reference mean of the two drug products.If the proportion of the confidence interval is greater than or equal to (1-2α)x100% and power is at least 80%, BE is concluded and the corresponding sample size can be determined[1, 9]. Generally; the simulation was performed using statistical software R. A different randomly selected seed was used for each scenario. A scenario was defined as a specified combination of ratio of geometric means, intra-subject coefficient of variation (CV), and sample size. The given parameters and assumptions in the simulation work are given in the following table.

Table 1. *The given parameters and assumptions in the simulation work*

μ_T	μ_R	$\theta=\frac{\mu_T}{\mu_R}$	**Sample size (n)**	σ_e^2	**CV%=** $\frac{\sigma_R}{\mu_R}\times100\%$
85		0.85	12	100	10
90		0.90	16	200	15
95		0.95	20	400	20
100	100	1.00	.	580	25
105		1.05	.	850	30
110		1.10	.	1200	35
115		1.15	100	1600	40
120		1.20	110	2000	45
			120	2500	50
			130	3000	55
			140		
			150		

μ_T = The true test mean

μ_R = The true references mean which is constant.

θ = Geometric mean ratio, thus, the equivalence limits for the difference are -20 to +20 and for the ratio are 0.8 and 1.25.

σ_e^2 = Intra-subject variability

And for a sample size n,

Test~N(μ_T, σ_T) and Reference~N(μ_R, σ_R)

Where, n, μ,σ are, respectively, the sample size, the true mean and the true standard deviation for the test and the reference drug products. One million simulated studies were performed at α=0.05 significant level. Note that, in our simulation results, the missing value is likely to be produced sometimes, if it is the case, it is replaced by the arithmetic mean of the other simulated data produced in each step. For all stages we evaluate BE based on the power approach for the given coefficient of variation (CV) and geometric mean ratio (GMR). Let us summarize this in the following figure. Note, for any clinical trial; a minimum of 12-sample size is required to conduct a study.

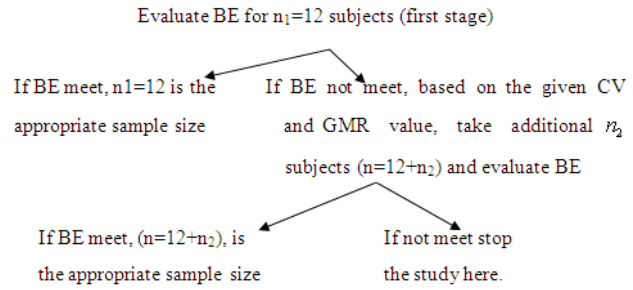

Figure 4. *Simple schematic presentation of simulation for determining sample size for BE*

3. Results and Discussions

For α=0.05, the proportion of the simulated value for all approaches should include at least 90% to conclude BE and the corresponding sample size to be sufficient, which was the aim of this work. Since the minimum sample size required to conduct any clinical study is 12, which is also

the initial sample size in our simulation study, 6, for each group.

For the given coefficient of variation and geometric mean ratios, the sample size determined from the simulation results is summarized in table 1 as follows.

Table 2. *Summary of sample size for the second stage are summarized from simulation results as follows*

	GMR=μT/μR							
CV%	**0.85**	**0.90**	**0.95**	**1.0**	**1.05**	**1.10**	**1.15**	**1.20**
10	52	8	0	0	0	0	12	88
15	60	12	0	0	0	8	8	
20	108	24	4	4	8	36	98	
25		36	12	8	28	60		
30		60	24	28	60			
35		98	40	40				
40			76	76				
45			118					
50								
55								

As shown from the simulation results in table 2 above, we can observe the required sample size needed to conduct a clinical trial when the *GMR=0.85* with the corresponding CV values. As a result when the GMR=0.85 and CV=10, we need additional 52 subjects, in addition to the initial sample size n=12. While for second stage, CV=15, additional 60 subjects are required to demonstrate BE (n=12+60). However, generally, we can observe that when CV increases from 10 to 15,we need additional 8 subjects, 4for each group. When the coefficient of variation increases from 10to 20, the sample size extremely increases to 108.Finally, for this GMR value there is no need of conducting any clinical trial for CV>20.

The summary of sample size for GMR=0.90 is also given in table 2 above and specifically, when the *GMR=0.90*, and CV=10, additional 8 subjects 4, subjects for each group, are important to achieve BE between the test and the reference drug products. For second stage, when CV=15, additional 12 samples are needed (n=12+12). From the results shown in the table, we can understand that for GMR=0.90 and CV=20, only 24 in addition to the initial 12 subjects, which is almost one third of the sample size required in case of GMR=0.85 for a constant CV values are needed to demonstrate BE. This implies that the sample size is highly affected by GMR, in addition to CV values. For GMR=0.9, for small values of (CV <30), a maximum of 48 subjects/ sample size is needed. In addition, for high values of CV≥ 30, a minimum of 72 subjects are needed to conduct a clinical study. However, when CV values (>35), proceeding to the next step/stage is not important. It may be harmful both ethically and economically as illustrated in the introduction part of this paper. Let us see the results when the *GMR=0.95*.The minimum number of sample size is achieved compared to the above two GMR values for a constant CV. Even, for CV=10 and 15, BE is achieved in the first stage which was not possible for the above two GMR values. For example, for CV=20, only 4 subjects are needed, 2 for each group. And here we go for other CV values similarly. To summarize, from the table given above, for small values of CV a maximum of 24 subjects are required, and for high values of CV, at least 36 subjects are needed. And for CV>40, we have to stop the study to protect wastage of resources.

When the *GMR=1.0*, and CV value is small, the simulation result shows similar sample size value with that of *GMR=0.95*.In addition, we stop the study when CV >40, which is the critical value of CV with the corresponding sample size = 88 .Nevertheless, for small values of CV, this GMR value is more appropriate in terms of sample size determinations than GMR=0.95. For example, when CV=25, 36 and 12 sample sizes are required to conduct a clinical trial for GMR=0.95 and 1.0, respectively.

When *GMR=1.05*, as we can see from table 2 above the simulation result shows that, for small values of CV, almost similar results of sample size is required with that of *GMR=0.95, and 1.0*. While for large values of CV, adding additional sample size is unimportant. In other words, we have to stop the study here and must use other alternatives. Specifically, for GMR 0.9 and 1.05, as we can see from table 2 above, for GMR=0.9 and for small values of CV more number of sample size is needed compared to GMR=1.05, while for large values of CV the reverse is true. In general, from the simulation results we can observe that, in order to determine the appropriate values of sample size, we have to see both GMR and CV values carefully.

And when the *GMR=1.10*, for small values of CV, the simulation result shows, approximately two times the number of subjects needed for *GMR=0.95,1.0,and 1.05*. However, when the variance becomes more heterogeneous, like CV>30 it is unimportant to conduct any trial for the given GMR=1.10; it is unethical as well as wastage of time and resource. For example, for CV=25, it is important to add 60(72=12+60) additional number of sample size to conduct BE study for the second stage. For *GMR=1.15*, the simulation result in table 2shows that based on the CV values, for the second stage, additional 12,32 and 98 subjects are required in addition to the 12 initial subjects. For example, when CV=10 a total of 24 (12+12) samples is required, but we have 12, which is the initial sample size for any clinical trial as we stated before. So, additional 12's are important.For simplicity, when CV is 20, we have to take additional 98 subjects/sample size in addition to the first 12.Finally, for GMR=1.20, for CV=10, the sample size is n=100, that is additional 88 samples are important. However, for CV>10, there is no need of taking additional sample size to conduct BE trials.

3.1. Summaries and Recommendations of the Study

In general, from our simulation study shown in table 2 above, we can understand that, for highly variable drugs (CV ≥ 30), the appropriate GMR value is between (0.95, 1.05), which is also appropriate for low variable drugs to achieve the minimum sample size required to conduct any clinical trials. For GMR values less than 0.95 and more than 1.05, we need a maximum number of subjects even for

low variable drug products. Finally, from our simulation result given in the appendix, we can observe that when the sample size increases, the proportion of (1-2α) x100% *Confidence* interval contained *in (0.8, 1.25)highly increases*, even for large values of CV and any values of GMR, but the value of *the power*, which is very important to detect meaningful clinical difference decreases. As a result, based on the power approach, demonstrating BE and determining the corresponding sample size for highly variable drugs and for GMR values out of the range (0.95, 1.05), is very difficult. Moreover, the other important thing here is that, as the intra-subject coefficient of variation (CV) increases, the power decreases and larger sample sizes are needed to achieve a given power. As a conclusion, from our simulation results we observed that, the appropriate GMR to conduct BE study is (0.95, 1.05), which is also recommended in FDA.

N.B: In the appendix part, the simulation result for samples (n=40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100 and 110) are not displayed in order to save the number of pages.

Acknowledgements

I would like to thank Prof. Dr. Mehmet N Orman, department head of Biostatistics and Bioinformatics, Ege University/Turkey/Izmir, for his advice and willingness to share his insightful thoughts with me, which was very fruitful for shaping up my ideas and the entire work.

Appendix

Simulation Results

		Proportions of Confidence interval values within (0.8, 1.25) for GMR							
Sample Size	**CV%**	**0.85**	**0.9**	**0.95**	**1**	**1.05**	**1.1**	**1.15**	**1.2**
12	10	0.337132	0.79513	0.980211	0.999023	0.989675	0.907737	0.63172	0.25143
	15	0.288505	0.6942	0.939016	0.979359	0.917381	0.733534	0.44006	0.17596
	20	0.237764	0.54664	0.791602	0.828852	0.697624	0.484785	0.27145	0.11821
	25	0.199152	0.42707	0.61646	0.648073	0.534291	0.360519	0.2043	0.09399
	30	0.137941	0.27285	0.390426	0.422639	0.360349	0.251608	0.14867	0.07541
	35	0.078729	0.14673	0.212633	0.241876	0.222583	0.169149	0.10955	0.06157
	40	0.042952	0.07755	0.113579	0.13575	0.135424	0.114181	0.08233	0.05159
	45	0.021422	0.04464	0.066492	0.082956	0.088025	0.080853	0.06376	0.04425
	50	0.01082	0.02594	0.038625	0.041	0.05641	0.056074	0.04961	0.03728
	55	0.006	0.02592	0.02505	0.033337	0.039236	0.041613	0.0393	0.03191
16	10	0.41769	0.8981	0.99694	0.99998	0.99856	0.98548	0.75036	0.31395
	15	0.36152	0.81775	0.98402	0.99695	0.97047	0.78491	0.53519	0.20858
	20	0.30562	0.68579	0.91906	0.92776	0.80637	0.76024	0.31864	0.12871
	25	0.2742	0.58973	0.80135	0.79429	0.64332	0.42879	0.22734	0.09728
	30	0.21809	0.4383	0.59088	0.58388	0.45522	0.29414	0.15718	0.07283
	35	0.14612	0.2694	0.36656	0.37499	0.30136	0.20103	0.11394	0.05702
	40	0.0854	0.15439	0.21419	0.23131	0.20025	0.14671	0.08906	0.04755
	45	0.05216	0.09094	0.13048	0.14976	0.13933	0.11049	0.07379	0.04326
	50	0.86303	0.005101	0.07708	0.09324	0.09584	0.0839	0.06104	0.03988
	55	0.8619	0.031182	0.04841	0.06345	0.06822	0.06504	0.05162	0.03794
20	10	0.48932	0.94869	0.99941	1	0.99989	0.98936	0.83487	0.36118
	15	0.4264	0.89318	0.99589	0.99954	0.99058	0.90878	0.61905	0.23328
	20	0. 36462	0.78657	0.96881	0.96905	0.87563	0.66227	0.36592	0.13448
	25	0.33611	0.70863	0.90035	0.89976	0.72089	0.49117	0.25469	0.09662
	30	0.29348	0.57603	0.72917	0.68611	0.52256	0.32973	0.16597	0.06785
	35	0.22	0.40157	0.50774	0.47456	0.35296	0.217	0.11454	0.05047
	40	0.14312	0.25137	0.32398	0.3138	0.2433	0.15578	0.0879	0.04143
	45	0.09126	0.15967	0.21163	0.22037	0.17851	0.12344	0.07364	0.03781
	50	0.03494	0.09522	0.1323	0.14676	0.13243	0.09899	0.06445	0.03754
	55	0.07877	0.06123	0.08918	0.10361	0.10069	0.08297	0.06008	0.03763
24	10	0.55189	0.97516	0.999936	10.999991	0.996757	0.89393	0.41241	0.04385
	15	0.48627	0.93734	0.999045	0.999953	0.997017	0.948593	0.69014	0.25995
	20	0.4216	0.83383	0.988332	0.986356	0.922052	0.726902	0.40889	0.14127
	25	0.3927	0.79003	0.951962	0.9362	0.781209	0.540547	0.27745	0.09836
	30	0.35945	0.6838	0.826074	0.754612	0.57049	0.35641	0.17514	0.06565
	35	0.29602	0.51933	0.616631	0.544549	0.387763	0.231894	0.11528	0.04655
	40	0.21059	0.35519	0.424296	0.380494	0.272415	0.163781	0.08439	0.03684
	45	0.14332	0.24128	0.297172	0.278279	0.207903	0.130415	0.07056	0.03262
	50	0.08877	0.15249	0.20125	0.199643	0.160872	0.108572	0.06314	0.03212
	55	0.05838	0.10283	0.18561	0.14968	0.130716	0.096126	0.05981	0.03375
28	10	0.60985	0.98842	0.99999	1	1	0.999	0.93151	0.45924
	15	0.54074	0.96535	0.99977	1	0.99919	0.97061	0.74738	0.14885
	20	0.47253	0.90387	0.9957	0.99417	0.95226	0.77964	0.44886	0.10047
	25	0.44435	0.85175	0.97732	0.95192	0.8276	0.59037	0.30202	0.06395
	30	0.41656	0.76628	0.88644	0.80508	0.61639	0.38623	0.18315	0.04269

		Proportions of Confidence interval values within (0.8, 1.25) for GMR							
Sample Size	**CV%**	**0.85**	**0.9**	**0.95**	**1**	**1.05**	**1.1**	**1.15**	**1.2**
	35	0.36386	0.61905	0.70046	0.59714	0.41522	0.23998	0.11503	0.03298
	40	0.27993	0.45374	0.50988	0.42847	0.28965	0.16526	0.0811	0.0288
	45	0.20419	0.32657	0.37342	0.3202	0.22341	0.13136	0.06615	0.02765
	50	0.13734	0.22176	0.26704	0.24289	0.17769	0.11019	0.05874	0.026
	55	0.09361	0.15735	0.19685	0.19134	0.15197	0.09917	0.05744	0
32	10	0.66483	0.99079	1	1	1	0.99958	0.95797	0.50271
	15	0.59433	0.98111	0.99992	1	0.99976	0.98455	0.79775	0.30845
	20	0.52356	0.93668	0.99839	0.99742	0.97011	0.82531	0.48643	0.15712
	25	0.49457	0.89626	0.98887	0.96863	0.868	0.63343	0.32637	0.10214
	30	0.47068	0.82858	0.92288	0.84339	0.65626	0.41319	0.19394	0.06267
	35	0.42738	0.70286	0.75771	0.64193	0.44069	0.25428	0.11622	0.04007
	40	0.35056	0.54126	0.57389	0.63822	0.30619	0.16928	0.0797	0.02903
	45	0.26944	0.40796	0.43804	0.63406	0.23381	0.13121	0.06293	0.02539
	50	0.19319	0.29246	0.32334	0.62015	0.18839	0.10847	0.05541	0.02419
	55	0.13765	0.21473	0.24869	0.55401	0.16482	0.1019	0.05291	0.02561
36	10	0.707958	0.99739	1	1	1	0.999903	0.97347	0.54625
	15	0.637613	0.9892	0.999989	1	0.99987	0.991753	0.83675	0.33564
	20	0.567312	0.95776	0.999401	0.998902	0.98212	0.862019	0.52543	0.16528
	25	0.538578	0.92546	0.994441	0.98028	0.89835	0.672854	0.34554	0.10392
	30	0.47068	0.87163	0.92288	0.84339	0.65626	0.41319	0.19394	0.06267
	35	0.484338	0.76703	0.806469	0.672334	0.47011	0.264885	0.11567	0.03816
	40	0.415692	0.61744	0.627598	0.493342	0.32254	0.17305	0.07555	0.02667
	45	0.335686	0.48727	0.491997	0.381844	0.24339	0.132191	0.05904	0.02242
	50	0.251044	0.36304	0.37816	0.300935	0.19714	0.109281	0.05231	0.02096
	55	0.18772	0.27846	0.303106	0.253997	0.1746	0.101106	0.05085	0.02254
120	10	0.98692	1	1	1	1	1	1	0.92623
	15	0.9718	1	1	1	1	1	0.99841	0.67541
	20	0.94776	1	1	1	0.99997	0.99889	0.89908	0.28757
	25	0.93658	0.99996	0.99999	1	0.9995	0.9704	0.65587	0.134
	30	0.93261	0.99967	0.99982	0.99721	0.96686	0.7681	0.3255	0.04816
	35	0.93421	0.99827	0.9924	0.95035	0.77931	0.43842	0.12775	0.01578
	40	0.93328	0.98795	0.94524	0.80213	0.52384	0.226	0.05422	0.00682
	45	0.92404	0.95821	0.85835	0.64668	0.36473	0.13903	0.03182	0.00434
	50	0.89519	0.90554	0.75631	0.51887	0.26597	0.09729	0.02256	0.00335
	55	0.85763	0.85656	0.68821	0.45017	0.22364	0.08427	0.0204	0.00399
130	10	0.99494	1	1	1	1	1	1	0.95695
	15	0.98747	1	1	1	1	1	0.99952	0.73984
	20	0.97262	1	1	1	1	0.99986	0.93675	0.31671
	25	0.96559	0.99997	1	0.99999	0.99971	0.98557	0.7168	0.14
	30	0.96332	0.99993	0.99997	0.99896	0.9826	0.82105	0.35746	0.04431
	35	0.96629	0.99958	0.9972	0.97109	0.83092	0.47895	0.13041	0.01369
	40	0.96686	0.99539	0.96759	0.85031	0.57178	0.24134	0.0525	0.00534
	45	0.9611	0.9777	0.90244	0.70066	0.39479	0.14285	0.02866	0.00323
	50	0.9445	0.94265	0.8108	0.56222	0.28336	0.09527	0.01997	0.0025
	55	0.91491	0.90415	0.74187	0.48855	0.23649	0.08041	0.01805	0.00229
140	10	0.99665	1	1	1	1	1	1	0.96772
	15	0.99088	1	1	1	1	1	0.99982	0.76793
	20	0.97992	1	1	1	1	0.9999	0.95025	0.33228
	25	0.97412	1	1	1	0.99988	0.98952	0.74384	0.14268
	30	0.97206	0.99999	0.99995	0.99946	0.98709	0.8445	0.37126	0.04376
	35	0.97336	0.99982	0.99814	0.97801	0.84959	0.49584	0.13138	0.01197
	40	0.97393	0.99721	0.97476	0.86973	0.59197	0.24786	0.05029	0.00429
	45	0.96968	0.98483	0.91747	0.72283	0.40788	0.14339	0.02691	0.00267
	50	0.95667	0.95352	0.83028	0.58215	0.29128	0.09414	0.01824	0.00223
	55	0.92612	0.91946	0.76382	0.50546	0.24373	0.07969	0.01604	0.00218
150	10	0.99811	1	1	1	1	1	1	0.97634
	15	0.99403	1	1	1	1	1	0.99992	0.79296
	20	0.9858	1	1	1	1	0.99993	0.99091	0.34727
	25	0.98159	1	1	1	0.99994	0.99316	0.76564	0.14857
	30	0.98009	0.99999	0.99999	0.99962	0.99094	0.86268	0.38576	0.04288
	35	0.98089	0.9994	0.99891	0.98368	0.86805	0.51673	0.13577	0.01157
	40	0.98076	0.99723	0.98179	0.88632	0.61578	0.25603	0.05015	0.00407
	45	0.97835	0.984	0.93013	0.74467	0.42661	0.14512	0.02632	0.00218
	50	0.96691	0.9558	0.84709	0.60225	0.30261	0.09521	0.01753	0.00164
	55	0.95059	0.91645	0.78544	0.52405	0.25088	0.07877	0.01559	0.00181

Continued to Simulation Results

		Corresponding power values for all values of mean ratio (GMR)							
Sample Size	**CV%**	**0.85**	**0.9**	**0.95**	**1**	**1.05**	**1.1**	**1.15**	**1.20 = (GMR)**
12	10	0.337132	0.56249	0.980211	0.999023	0.989675	0.907737	0.63172	0.25143
	15	0.009471	0.26495	0.980722	0.998079	0.992461	0.844657	0.22483	0.00154
	20	0.002156	0.06563	0.841966	0.950614	0.888476	0.492769	0.05747	0.00015
	25	0.000307	0.002389	0.436652	0.633913	0.488147	0.140131	0.00774	1.00E-05
	30	9.00E-05	0.00703	0.22278	0.375481	0.25279	0.052589	0.00208	1.00E-05
	35	8.00E-05	0.00221	0.089261	0.171257	0.102133	0.015858	0.00073	0
	40	5.00E-06	0.00227	0.033896	0.071018	0.038863	0.004897	0.00015	0
	45	1.00E-06	0.00042	0.014677	0.032707	0.016765	0.001948	4.00E-05	0
	50	0	0.00037	0.004971	0.012	0.005353	6.00E-04	0	0
	55	0	0.00032	0.003308	0.007886	0.003838	0.000428	0	0
16	10	0.01318	0.85141	0.99694	1	0.99998	0.98546	0.44059	0.00136
	15	0.0022	0.50486	0.98402	0.99794	0.9912	0.78368	0.11077	1.00E-05
	20	0.00014	0.12521	0.91906	0.8791	0.76352	0.27329	0.01046	0
	25	2.00E-05	0.03821	0.40993	0.62199	0.64567	0.09368	0.00196	0
	30	0	0.00875	0.16369	0.30804	0.18558	0.02369	0.00026	0
	35	0	0.00187	0.05552	0.12366	0.06451	0.00536	7.00E-05	0
	40	0	0.00061	0.02019	0.0513	0.02428	0.00165	2.00E-05	0
	45	0	0.00026	0.0097	0.02574	0.01151	0.00073	1.00E-05	0
	50	0	0.00012	0.00489	0.01346	0.00611	0.00028	1.00E-05	0
	55	0	6.00E-05	0.00291	0.00897	0.00393	0.00016	0	0
20	10	0.02289	0.97568	1	1	1	0.99971	0.70234	0.000134
	15	0.00289	0.7571	0.99931	0.99999	0.99972	0.95005	0.21705	3.00E-05
	20	0.00013	0.23392	0.90237	0.97442	0.92576	0.46772	0.01658	0
	25	1.00E-05	0.07019	0.63045	0.82361	0.67898	0.1737	0.00024	0
	30	0	0.01374	0.28196	0.48554	0.31975	0.03858	0	0
	35	0	0.00267	0.09389	0.20612	0.10731	0.0078	0	0
	40	0	0.00063	0.03211	0.08147	0.03708	0.00191	0	0
	45	0	0.00023	0.01402	0.03909	0.01611	0.00065	0	0
	50	0	0.00013	0.00657	0.01901	0.00029	0	0	0
	55	0	8.00E-05	0.00387	0.01143	0.00396	0.00021	0	0
24	10	0.99852	1	1	1	0.999999	0.89465	0.00242	
	15	0.0451	0.92375	0.999979	1	0.999995	0.993572	0.37952	4.00E-05
	20	8.00E-05	0.39902	0.975339	0.995362	0.982824	0.678704	0.03043	0
	25	0	0.12569	0.808073	0.995363	0.840534	0.295894	0.00387	0
	30	0	0.02316	0.432194	0.653015	0.473073	0.06907	0.00028	0
	35	0	0.00367	0.154681	0.313356	0.176845	0.01234	3.00E-05	0
	40	0	0.00073	0.051792	0.130473	0.060602	0.00762	0	0
	45	0	0.00019	0.020824	0.060623	0.024726	0.002512	0	0
	50	0	7.00E-05	0.028617	0.010787	0.000825	0.000293	0	0
	55	0	3.00E-05	0.016423	0.005839	0.000293	0.000146	0	0
28	10	0.08418	0.99996	1	1	1	1	0.97824	0.00408
	15	0.00784	0.98559	1	1	1	0.99967	0.58388	3.00E-05
	20	0.00018	0.59061	0.99456	0.99913	0.99656	0.84323	0.05511	0
	25	1.00E-05	0.21803	0.91387	0.97445	0.92995	0.45261	0.00625	0
	30	0	0.04015	0.58908	0.78471	0.62521	0.11671	0.00035	0
	35	0	0.00567	0.23487	0.4354	0.26392	0.01964	0	0
	40	0	0.00074	0.08049	0.19403	0.09431	0.00381	0	0
	45	0	0.00021	0.03176	0.09033	0.03782	0.00099	0	0
	50	0	9.00E-05	0.01346	0.0427	0.015	0.00023	0	0
	55	0	3.00E-05	0.00698	0.02349	0.00745	0.00015	0	0
32	10	0.15689	1	1	1	1	1	0.99724	0.00742
	15	0.01451	0.99817	1	1	1	1	0.77113	8.00E-05
	20	0.00018	0.76157	0.99878	0.9997	0.99913	0.93714	0.10002	0
	25	1.00E-05	0.33786	0.963	0.98898	0.97078	0.61272	0.01109	0
	30	0	0.06656	0.71805	0.87095	0.74882	0.18586	0.00062	0
	35	0	0.00852	0.33091	0.55203	0.36734	0.03269	2.00E-05	0
	40	0	0.00122	0.12074	0.55089	0.13811	0.00552	1.00E-05	0
	45	0	0.00033	0.04781	0.55076	0.05629	0.00139	1.00E-05	0
	50	0	6.00E-05	0.01907	0.5321	0.02242	3.00E-04	0	0
	55	0	4.00E-05	0.00905	0.25664	0.01174	0.00017	0	0
36	10	0.263753	1	1	1	1	1	0.99977	0.01315
	15	0.027538	0.99983	1	1	1	0.999997	0.90215	7.00E-05
	20	0.000346	0.88541	0.999578	0.999873	0.99974	0.978222	0.17142	0

		Corresponding power values for all values of mean ratio (GMR)							
Sample Size	**CV%**	**0.85**	**0.9**	**0.95**	**1**	**1.05**	**1.1**	**1.15**	**1.20 = (GMR)**
	25	5.00E-06	0.48738	0.984359	0.995091	0.98727	0.7531	0.02005	0
	30	0	0.11288	0.71805	0.87095	0.74882	0.18586	0.00062	0
	35	0	0.01438	0.437992	0.656194	0.47434	0.052066	6.00E-05	0
	40	0	0.00181	0.173676	0.352129	0.19769	0.008747	3.00E-05	0
	45	0	0.00031	0.071183	0.182467	0.08216	0.002095	1.00E-05	0
	50	0	0.00011	0.027972	0.087753	0.03328	0.000542	0	0
	55	0	4.00E-05	0.013599	0.048259	0.01604	0.000185	0	0
120	10	1	1	1	1	1	1	1	1
	15	1	1	1	1	1	1	1	0.8349
	20	0.88763	1	1	1	1	1	0.99992	0.00133
	25	0.17437	0.99969	0.99997	0.99999	1	0.99991	0.99313	0
	30	0.00126	0.9905	0.99957	0.99989	0.99956	0.99555	0.71564	0
	35	0	0.87882	0.99655	0.99873	0.99659	0.94746	0.09856	0
	40	0	0.51437	0.97904	0.99415	0.98274	0.73053	0.00316	0
	45	0	0.20538	0.93169	0.97986	0.9399	0.42967	0.00011	0
	50	0	0.05494	0.82774	0.94182	0.84636	0.18307	1.00E-05	0
	55	0	0.01648	0.70057	0.89119	0.73147	0.07527	0	0
130	10	1	1	1	1	1	1	1	1
	15	1	1	1	1	1	1	1	0.8349
	20	0.88763	1	1	1	1	1	0.99992	0.00133
	25	0.17437	0.99975	0.99997	0.99999	1	0.99991	0.99313	0
	30	0.00126	0.99428	0.99957	0.99989	0.99956	0.99555	0.71564	0
	35	0	0.92166	0.99655	0.99873	0.99659	0.94746	0.09856	0
	40	0	0.61774	0.97904	0.99415	0.98274	0.73053	0.00316	0
	45	0	0.2914	0.93169	0.97986	0.9399	0.42967	0.00011	0
	50	0	0.09072	0.82774	0.94182	0.84636	0.18307	1.00E-05	0
	55	0	0.03002	0.78881	0.93485	0.81055	0.11801	0	0
140	10	1	1	1	1	1	1	1	1
	15	1	1	1	1	1	1	1	0.94943
	20	0.96354	1	1	1	1	0.99999	0.99996	0.00045
	25	0.31707	0.99983	1	1	1	0.99994	0.99633	0
	30	0.00352	0.99653	0.99978	0.99994	0.99998	0.99737	0.81752	0
	35	1.00E-05	0.94908	0.99798	0.99944	0.99974	0.96708	0.16339	0
	40	0	0.71167	0.98869	0.99684	0.99009	0.80704	0.00739	0
	45	0	0.38156	0.95874	0.99	0.96393	0.53232	0.00031	0
	50	0	0.13776	0.88588	0.96851	0.89943	0.25537	1.00E-05	0
	55	0	0.04811	0.70057	0.89119	0.73147	0.07527	0	0
150	10	1	1	1	1	1	1	1	1
	15	1	1	1	1	1	1	1	0.99864
	20	0.99759	1	1	1	1	1	0.99999	0.03543
	25	0.66565	0.99987	0.99999	1	1	0.99997	0.9983	1.00E-05
	30	0.02197	0.99657	0.99995	0.99998		0.9989	0.92682	0
	35	2.00E-05	0.94788	0.99944	0.9999	0.99995	0.98662	0.34984	0
	40	0	0.71414	0.99663	0.99916	0.99958	0.90667	0.02793	0
	45	0	0.38166	0.9861	0.99721	0.99689	0.71191	0.0014	0
	50	0	0.13744	0.9566	0.97882	0.98886	0.43301	6.00E-05	0
	55	0	0.04854	0.90774	0.95321	0.96278	0.24025	0	0

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