```
# calculate upper 90% CL
ul <- exp(y11+y6*y12)
# test for failure
nc10 <- 0
nc25 <- 0
if(ll<.9||ul>1.10){nc10<-1}
if(ll<.8||ul>1.25){nc25<-1}
# calculate index for lcmxex matrix
idx <- nreps-z+1
# save individual results in lcmxex
lcmxex[idx,] <- c(exp(y8),exp(y10),exp(y11),ll,ul,nc10,nc25,cdiff,nzy)
# count failures
lcmxen10 <- lcmxen10+nc10
lcmxen25 <- lcmxen25+nc25
# perform anova for log transformed observed AUC, LAUCO
y1 <- aov(LAUCO~TRT+PD+SEQ+CID%in%SEQ,y)
y2 <- summary(y1)
# get error term
y3 <- y2[5,3]
# calculate standard error
y6 <- sqrt(as.numeric(y3)*2/n2)
# calculate means
trt <- y[,"TRT"]=="1"
y8 <- mean(y[trt,"LAUCO"])
y10 <- mean(y[!trt,"LAUCO"])
# calculate difference
y11 <- (y8-y10)
# get quantile
y12 <- qt(p,df)
# calculate lower 90% CL
ll <- exp(y11-y6*y12)
# calculate upper 90% CL
ul <- exp(y11+y6*y12)
# test for failure
nc10 <- 0
nc25 <- 0
if(ll<.9||ul>1.10){nc10<-1}
if(ll<.8||ul>1.25){nc25<-1}
# calculate index for lauco matrix
idx <- nreps-z+1
# save individual results in lauco
lauco[idx,] <- c(exp(y8),exp(y10),exp(y11),ll,ul,nc10,nc25,cdiff,nzy)
# count failures
```

```
laucon10 <- laucon10+nc10
laucon25 <- laucon25+nc25
# perform anova for log transformed baseline corrected(M1) AUC, LAUCEX
y1 <- aov(LAUCEX~TRT+PD+SEQ+CID%in%SEQ,y)
y2 <- summary(y1)
# get error term
y3 <- y2[5,3]
# calculate standard error
y6 <- sqrt(as.numeric(y3)*2/n2)
# calculate means
trt <- y[,"TRT"]=="1"
y8 <- mean(y[trt,"LAUCEX"])
y10 <- mean(y[!trt,"LAUCEX"])
# calculate difference
y11 <- (y8-y10)
# get quantile
y12 <- qt(p,df)
# calculate lower 90% CL
ll <- exp(y11-y6*y12)
# calculate upper 90% CL
ul <- exp(y11+y6*y12)
# test for failure
nc10 <- 0
nc25 <- 0
if(ll<.9||ul>1.10){nc10<-1}
if(ll<.8||ul>1.25){nc25<-1}
# calculate index for laucex matrix
idx <- nreps-z+1
# save individual results in laucex
laucex[idx,] <- c(exp(y8),exp(y10),exp(y11),ll,ul,nc10,nc25,cdiff,nzy)
# count failures
laucen10 <- laucen10+nc10
laucen25 <- laucen25+nc25
# decrement loop counter
z <- z-1
}
# print data file for last replication
write.table(y,paste(filenm,"final.y.matrix.csv",sep = ""),sep = ",",dimnames.write =
   "colnames")

#
#  Make headers for each file on 1st iteration of j and i loops
#

if (j == 1 & i == 1)
{
#  LCMXO
header <-
   paste("Cmax.test","Cmax.ref","mean.diff","LCI90","UCI90","nc10","nc25","tx.diff","n
   ",sep = ",")
write.table(header,paste(filenm,"lcmxo.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = F)

#  LCMXEX
header <-
   paste("Cmax.test","Cmax.ref","mean.diff","LCI90","UCI90","nc10","nc25","tx.diff","n
   ",sep = ",")
write.table(header,paste(filenm,"lcmxex.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = F)
```

```
#  LAUCO
header <-
   paste("AUC.test","AUC.ref","mean.diff","LCI90","UCI90","nc10","nc25","tx.diff","n",
   sep = ",")
write.table(header,paste(filenm,"lauco.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = F)

#  LAUCEX
header <-
   paste("AUC.test","AUC.ref","mean.diff","LCI90","UCI90","nc10","nc25","tx.diff","n",
   sep = ",")
write.table(header,paste(filenm,"laucex.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = F)

#  Summary file
header <-
   paste("Run","tx.diff","n","lcmxon10","laucon10","lcmxon25","laucon25","lcmxen10","l
   aucen10",
"lcmxen25","laucen25",sep = ",")
write.table(header, paste(filenm,"sim.summary.m2.csv",sep = ""),sep =
   ",",dimnames.write = "colnames",append = F)
}


#  Write files containing the results of each replicate
write.table(lcmxo,paste(filenm,"lcmxo.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = T)
write.table(lcmxex,paste(filenm,"lcmxex.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = T)
write.table(lauco,paste(filenm,"lauco.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = T)
write.table(laucex,paste(filenm,"laucex.m2.csv",sep = ""),sep = ",",dimnames.write =
   "colnames",append = T)

#  Create summary file
xxx1[1,]<-
   c(run,cdiff,n2,lcmxon10,laucon10,lcmxon25,laucon25,lcmxen10,laucen10,lcmxen25,lauce
   n25)
write.table(xxx1, paste(filenm,"sim.summary.m2.csv",sep = ""),sep = ",",dimnames.write
   = "colnames",append = T)
}
#}
```

Appendix IV. Tabulation of Simulation Results (Expressed as number of failed trials out of 1000 replications.)

Simulations for Method 1
Run is an index for the fractional difference in extent of absorption, Test - Reference
Diff is the fractional difference in extent of absorption, Test - Reference
N is the sample size

			Baseline Uncorrected				Baseline Corrected - Method 1			
			90 - 110%		80 - 125%		90 - 110%		80 - 125%	
			Total trials out of 1000 replications that fail BE criteria							
Run	Diff	N	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48
1	-0.5	24	1000	1000	1000	165	1000	1000	1000	1000
2	-0.45	24	1000	1000	991	24	1000	1000	1000	1000
3	-0.4	24	1000	1000	846	2	1000	1000	1000	1000
4	-0.35	24	1000	994	387	0	1000	1000	1000	1000
5	-0.33	24	1000	968	202	0	1000	1000	1000	1000
6	-0.3	24	1000	897	64	0	1000	1000	1000	1000
7	-0.25	24	992	640	5	0	1000	1000	999	995
8	-0.2	24	897	314	0	0	1000	1000	935	937
9	-0.15	24	584	100	0	0	996	996	646	745
10	-0.1	24	164	17	0	0	937	978	176	401
11	-0.05	24	24	2	0	0	765	939	21	146
12	0	24	9	0	0	0	600	937	1	59
13	0.05	24	80	10	0	0	787	948	18	125
14	0.1	24	324	60	0	0	955	984	130	342
15	0.15	24	706	234	0	0	999	996	430	620
16	0.2	24	931	502	0	0	1000	999	784	825
17	0.25	24	991	756	0	0	1000	1000	954	949
18	0.3	24	999	916	27	0	1000	1000	996	986
19	0.33	24	1000	966	69	0	1000	1000	1000	996
20	0.35	24	1000	980	129	0	1000	1000	1000	998
21	0.4	24	1000	995	355	0	1000	1000	1000	999
22	0.45	24	1000	1000	682	12	1000	1000	1000	1000
23	0.5	24	1000	1000	889	39	1000	1000	1000	1000

			Baseline Uncorrected				Baseline Corrected - Method 1			
			90 - 110%		80 - 125%		90 - 110%		80 - 125%	
			Total trials out of 1000 replications that fail BE criteria							
Run	Diff	N	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48
1	-0.5	36	1000	1000	1000	41	1000	1000	1000	1000
2	-0.45	36	1000	1000	997	2	1000	1000	1000	1000
3	-0.4	36	1000	1000	837	0	1000	1000	1000	1000
4	-0.35	36	1000	993	253	0	1000	1000	1000	1000
5	-0.33	36	1000	977	90	0	1000	1000	1000	1000
6	-0.3	36	1000	895	14	0	1000	1000	1000	1000
7	-0.25	36	997	548	0	0	1000	1000	998	999
8	-0.2	36	910	144	0	0	1000	1000	956	953
9	-0.15	36	459	24	0	0	998	998	530	645
10	-0.1	36	69	1	0	0	957	962	79	227
11	-0.05	36	5	0	0	0	605	806	4	41
12	0	36	2	0	0	0	348	741	0	6
13	0.05	36	13	0	0	0	641	852	2	33
14	0.1	36	167	10	0	0	943	959	37	186
15	0.15	36	575	91	0	0	997	992	293	527
16	0.2	36	902	358	0	0	1000	1000	681	802
17	0.25	36	995	699	0	0	1000	1000	942	948
18	0.3	36	1000	910	3	0	1000	1000	995	991
19	0.33	36	1000	967	12	0	1000	1000	999	997
20	0.35	36	1000	982	31	0	1000	1000	999	1000
21	0.4	36	1000	1000	213	0	1000	1000	1000	1000
22	0.45	36	1000	1000	549	1	1000	1000	1000	1000
23	0.5	36	1000	1000	850	7	1000	1000	1000	1000

			Baseline Uncorrected				Baseline Corrected - Method 1			
			90 - 110%		80 - 125%		90 - 110%		80 - 125%	
			Total trials out of 1000 replications that fail BE criteria							
Run	Diff	N	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48
1	-0.5	48	1000	1000	1000	9	1000	1000	1000	1000
2	-0.45	48	1000	1000	998	0	1000	1000	1000	1000
3	-0.4	48	1000	1000	800	0	1000	1000	1000	1000
4	-0.35	48	1000	997	141	0	1000	1000	1000	1000
5	-0.33	48	1000	979	32	0	1000	1000	1000	1000
6	-0.3	48	1000	898	2	0	1000	1000	1000	1000
7	-0.25	48	1000	466	0	0	1000	1000	1000	999
8	-0.2	48	903	76	0	0	1000	1000	951	952
9	-0.15	48	339	2	0	0	1000	999	408	607
10	-0.1	48	19	0	0	0	951	952	21	135
11	-0.05	48	0	0	0	0	492	695	0	9
12	0	48	0	0	0	0	162	493	0	1
13	0.05	48	2	0	0	0	580	741	0	6
14	0.1	48	79	0	0	0	943	947	8	79
15	0.15	48	495	29	0	0	998	995	181	371
16	0.2	48	903	206	0	0	1000	1000	648	755
17	0.25	48	997	603	0	0	1000	1000	943	945
18	0.3	48	1000	910	0	0	1000	1000	997	995
19	0.33	48	1000	975	1	0	1000	1000	1000	998
20	0.35	48	1000	989	7	0	1000	1000	1000	1000
21	0.4	48	1000	1000	107	0	1000	1000	1000	1000
22	0.45	48	1000	1000	466	0	1000	1000	1000	1000
23	0.5	48	1000	1000	847	0	1000	1000	1000	1000

Simulations for Method 2
Run is an index for the fractional difference in extent of absorption, Test - Reference
Diff is the fractional difference in extent of absorption, Test - Reference
N is the sample size

			Baseline Uncorrected				Baseline Corrected - Method 2			
			90 - 110%		80 - 125%		90 - 110%		80 - 125%	
			Total trials out of 1000 replications that fail BE criteria							
Run	Diff	N	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48
1	-0.5	24	1000	1000	1000	839	1000	1000	1000	1000
2	-0.45	24	1000	1000	995	360	1000	1000	1000	1000
3	-0.4	24	1000	1000	891	51	1000	1000	1000	1000
4	-0.35	24	1000	1000	435	4	1000	1000	1000	1000
5	-0.33	24	1000	1000	249	0	1000	1000	1000	1000
6	-0.3	24	1000	993	64	0	1000	1000	1000	1000
7	-0.25	24	996	904	1	0	1000	1000	1000	999
8	-0.2	24	938	561	0	0	1000	1000	955	952
9	-0.15	24	580	169	0	0	1000	998	602	662
10	-0.1	24	181	33	0	0	956	959	155	228
11	-0.05	24	23	2	0	0	701	780	14	32
12	0	24	2	0	0	0	541	687	0	4
13	0.05	24	49	6	0	0	773	820	12	25
14	0.1	24	312	71	0	0	957	958	103	153
15	0.15	24	697	319	0	0	998	993	425	484
16	0.2	24	923	677	0	0	1000	1000	782	791
17	0.25	24	990	918	1	0	1000	1000	955	948
18	0.3	24	1000	984	15	0	1000	1000	998	991
19	0.33	24	1000	997	50	0	1000	1000	999	998
20	0.35	24	1000	999	109	2	1000	1000	1000	998
21	0.4	24	1000	1000	366	9	1000	1000	1000	1000
22	0.45	24	1000	1000	690	62	1000	1000	1000	1000
23	0.5	24	1000	1000	902	217	1000	1000	1000	1000

			Baseline Uncorrected				Baseline Corrected - Method 2			
			90 - 110%		80 - 125%		90 - 110%		80 - 125%	
			Total trials out of 1000 replications that fail BE criteria							
Run	Diff	N	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48
1	-0.5	36	1000	1000	1000	792	1000	1000	1000	1000
2	-0.45	36	1000	1000	997	215	1000	1000	1000	1000
3	-0.4	36	1000	1000	843	10	1000	1000	1000	1000
4	-0.35	36	1000	1000	280	0	1000	1000	1000	1000
5	-0.33	36	1000	1000	103	0	1000	1000	1000	1000
6	-0.3	36	1000	996	14	0	1000	1000	1000	1000
7	-0.25	36	997	889	0	0	1000	1000	1000	1000
8	-0.2	36	913	424	0	0	1000	1000	954	952
9	-0.15	36	460	46	0	0	1000	1000	489	540
10	-0.1	36	68	3	0	0	954	952	54	96
11	-0.05	36	2	0	0	0	561	618	0	5
12	0	36	1	0	0	0	274	380	0	0
13	0.05	36	14	0	0	0	643	686	0	5
14	0.1	36	168	20	0	0	946	958	24	60
15	0.15	36	598	183	0	0	999	997	260	326
16	0.2	36	925	577	0	0	1000	1000	693	719
17	0.25	36	996	922	0	0	1000	1000	946	958
18	0.3	36	1000	989	4	0	1000	1000	996	996
19	0.33	36	1000	999	17	0	1000	1000	1000	1000
20	0.35	36	1000	1000	33	0	1000	1000	1000	1000
21	0.4	36	1000	1000	224	1	1000	1000	1000	1000
22	0.45	36	1000	1000	582	13	1000	1000	1000	1000
23	0.5	36	1000	1000	885	110	1000	1000	1000	1000

			Baseline Uncorrected				Baseline Corrected - Method 2			
			90 - 110%		80 - 125%		90 - 110%		80 - 125%	
			Total trials out of 1000 replications that fail BE criteria							
Run	Diff	N	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48	Cmax	AUC0_48
1	-0.5	48	1000	1000	1000	747	1000	1000	1000	1000
2	-0.45	48	1000	1000	999	101	1000	1000	1000	1000
3	-0.4	48	1000	1000	825	0	1000	1000	1000	1000
4	-0.35	48	1000	1000	156	0	1000	1000	1000	1000
5	-0.33	48	1000	1000	41	0	1000	1000	1000	1000
6	-0.3	48	1000	996	0	0	1000	1000	1000	1000
7	-0.25	48	1000	877	0	0	1000	1000	1000	1000
8	-0.2	48	891	302	0	0	1000	1000	937	952
9	-0.15	48	340	18	0	0	1000	1000	346	449
10	-0.1	48	24	0	0	0	937	952	15	36
11	-0.05	48	0	0	0	0	445	529	0	0
12	0	48	0	0	0	0	141	178	0	0
13	0.05	48	3	0	0	0	575	602	0	0
14	0.1	48	95	6	0	0	950	955	10	13
15	0.15	48	530	88	0	0	1000	998	168	202
16	0.2	48	925	476	0	0	1000	1000	653	664
17	0.25	48	998	909	0	0	1000	1000	950	955
18	0.3	48	1000	997	0	0	1000	1000	999	997
19	0.33	48	1000	999	3	0	1000	1000	1000	1000
20	0.35	48	1000	1000	13	0	1000	1000	1000	1000
21	0.4	48	1000	1000	137	0	1000	1000	1000	1000
22	0.45	48	1000	1000	526	4	1000	1000	1000	1000
23	0.5	48	1000	1000	879	42	1000	1000	1000	1000