BIOS668 HW#3
Honor Pledge: On my honor, I have neither given nor received unauthorized aid on this assignment.
Sara O'Brien

Q1. Full SAS code and output attached.

	% MTD	Mean Number of Patients	Mean Number of DLTs
Dose Level 1	12.87	3.55	0.26
Dose Level 2	17.12	3.62	0.45
Dose Level 3	21.58	3.24	0.50
Dose Level 4	29.77	2.71	0.57
Dose Level 5	13.34	1.95	0.70
Dose Level 6	5.32	0.75	0.31

Q2. Full SAS code and output attached.

(1) Single-stage design with minimal sample size: This study is designed as a single-stage phase II study. The null hypothesis is H0: $p \leq 0.3$ vs H1: $p > 0.6$ where p is the response rate. The smallest sample size meeting requirements of 80% power at an alpha level of 0.10 is 14 patients with a cutoff of 6 patients. The Type I Error, or probability of accepting a poor drug, is 0.09 and the power, or probability of rejecting a good drug, is 0.85.

Relevant SAS Code:

```
160  ****************************************************************
161  Question 2.1: find the single-stage design with minimal sample size
162  ****************************************************************;
163
164  /* Single stage */
165  %macro one_stage(
166  p0= , /* Unacceptable response */
167  p1= , /* Acceptable response */
168  alpha= , /* Type I Error (probability of accepting a poor drug) */
169  beta= , /* 1-Power (probability of rejecting a good drug) */
170  usern=  /* User-specified maximum sample size */
171  );
172
173  DATA one_stage_output;
174    RETAIN low_n 0 p0 0 p1 0 alpha 0 beta 0 stat 0;
175
176    p0=&p0; p1=&p1; alpha=&alpha; beta=&beta;
177    low_n = INT( 0.25*(p0+p1)*(2-p0-p1)*( ( ( quantile('NORMAL', 1-alpha)+ quantile('NORMAL', 1-beta))/
178    (p1-p0))**2));
179
180    DO n = low_n to &usern;  /* Total sample size */
181      DO r = 0 to n; /* Stage 1 cut-off */
182        term1_p0 = cdf('BINOMIAL', r, &p0, n);
183        term1_p1 = cdf('BINOMIAL', r, &p1, n);
184        if (term1_p1 <=  &beta and 1-term1_p0<=&alpha) then output;
185      END;
186    END;
187  RUN;
188  %mend one_stage;
189
190  %one_stage(p0=0.30,p1=0.60,alpha=0.10,beta=0.20,usern=80);
191
192  DATA result_singlestage;
193    SET one_stage_output;
194    real_alpha = 1-(term1_p0);
195    real_beta = (term1_p1);
196    KEEP alpha beta p0 p1 n r real_alpha real_beta;
197  RUN;
198
199  PROC SORT DATA = result_singlestage;
200    BY n;
201  RUN;
202
203  proc print data = result_singlestage (obs=1);
204      title 'Single-stage design with minimal sample size';
205  run;
```

Relevant SAS Output:

Single-stage design with minimal sample size

Obs	p0	p1	alpha	beta	n	r	real_alpha	real_beta
1	0.3	0.6	0.1	0.2	14	6	0.093282	0.15014

Optimal Simon's 2-stage design: The protocol has a standard Simon two stage design. The null hypothesis that the true response rate is 0.3 will be tested against a one-sided alternative. In the first stage, 5 patients will be accrued. If there are 1 or less responses in these patients, the study will be stopped. Otherwise, 9 additional patients will be accrued for a total of 14. The null hypothesis will be rejected if 7 or more responses are observed in 14 patients. This design yields a Type I Error rate, or probability of accepting a poor drug, of 0.083 and power, or probability of rejecting a good drug, of 0.81 when the true response rate is 0.6.

Relevant SAS Code:

```
207  ****************************************************
208  Question 2.1: find the Optimal Simon's 2-stage design
209  ****************************************************;
210
211  /* Simon's two-stage */
212  %macro simon_twostage(
213  p0= , /* Unacceptable response */
214  p1= , /* Acceptable response */
215  alpha= , /* Type I Error (probability of accepting a poor drug) */
216  beta= , /* 1-Power (probability of rejecting a good drug) */
217  usern=  /* User-specified maximum sample size */
218  );
219
220  DATA simon_twostage;
221    RETAIN low_n 0 p0 0 p1 0 alpha 0 beta 0 stat 0;
222
223    p0=&p0; p1=&p1; alpha=&alpha; beta=&beta;
224    low_n = INT( 0.25*(p0+p1)*(2-p0-p1)*( ( ( quantile('NORMAL', 1-alpha)+ quantile('NORMAL', 1-beta))/(p1-p0)
225    )**2));
226
227    DO n = low_n to &usern;  /* Total sample size */
228      DO n1 = 1 to n-1;  /* Stage 1 Sample size */
229        DO r1 = 0 to n1; /* Stage 1 cut-off */
230          term1_p0 = cdf('BINOMIAL', r1, &p0, n1);
231          term1_p1 = cdf('BINOMIAL', r1, &p1, n1);
232          if term1_p1=<&beta then DO; /*remove solution sets that do not meet the beta requirement*/
233            stat = 0;
234            DO r = n to r1 BY - 1 WHILE (stat=0);
235              term2_p0=0; *initialize the summation terms for alpha & beta calculations;
236              term2_p1=0;
237              do x=r1+1 to min(r, n1);
238                dum0=pdf('BINOMIAL', x, &p0, n1)*cdf('BINOMIAL', r-x, &p0, n-n1);
239                dum1=pdf('BINOMIAL', x, &p1, n1)*cdf('BINOMIAL', r-x, &p1, n-n1);
240                term2_p0= term2_p0 + dum0;
241                term2_p1= term2_p1 + dum1;
242              end;
243              if 1-(term1_p0+term2_p0)=<&alpha and (term1_p1+term2_p1)=<&beta then DO;
```

```
244
245  output; stat = 1; END;
246                    END;
247                  END;
248       END;
249     END;
250   END;
251  RUN;
252  %mend simon_twostage;
253
254  %simon_twostage(
255  p0=0.30,   /* Unacceptable response */
256  p1=0.60,   /* Acceptable response */
257  alpha=0.10,  /* Type I Error (probability of accepting a poor drug) */
258  beta=0.20,   /* 1-Power (probability of rejecting a good drug) */
259  usern=80   /* User-specified maximum sample size */
260  );
261
262  DATA result_twostage;
263    SET simon_twostage;
264    real_alpha = 1-(term1_p0+term2_p0);
265    real_beta = (term1_p1+term2_p1);
266    PET = term1_p0;
267    EN = n1+(1-PET)*(n-n1);
268    KEEP alpha beta p0 p1 n1 r1 n r real_alpha real_beta PET EN;
269  RUN;
270
271  PROC SORT DATA = result_twostage;
272    BY EN;
273  RUN;
274
275  proc print data = result_twostage (obs=1);
276      title 'Optimal Simon's 2-stage design';
277  run;
```

Relevant SAS Output:

Optimal Simon's 2-stage design

Obs	p0	p1	alpha	beta	n	n1	r1	r	real_alpha	real_beta	PET	EN
1	0.3	0.6	0.1	0.2	14	5	1	6	0.083451	0.18958	0.52822	9.24602

(2) The simulation verifies the single-stage design from 2.1 since the simulated Type I Error, 0.0974, and simulated power, 0.84, are close to the desired requirements of 0.10 and 0.80 (1-.20) respectively.

Relevant SAS Code:

```
279  ********************************************************
280  Question 2.2: Simulate single-stage studies and use the
281  code to verify the design in (2.1).
282  ********************************************************;
283
284  data sim1;
285      call streaminit(730317945);
286
287      type1 = 0;
288      power = 0;
289
290      do rep=1 to 5000;
291          null = rand('Binom', .3, 14);
292          if null>6 then type1=type1+(1/5000);
293          else type1=type1;
294          alt = rand('Binom', .6, 14);
295          if alt>6 then power=power+(1/5000);
296          else power=power;
297      end;
298  run;
299
300  proc print data=sim1;
301      title 'Type I Error and Power of 1-stage simulation';
302      var type1 power;
303  run;
```

Relevant SAS Output:

Type I Error and Power of 1-stage simulation

Obs	type1	power
1	0.0974	0.843

(3) The simulation verifies the Optimal Simon's 2-stage design from 2.1 since the simulated Type I Error, 0.0824, and simulated power, 0.798, are close to the desired requirements of 0.10 and 0.80 respectively.

Relevant SAS Code:

```
305  ********************************************************
306  Question 2.3: Simulate Simon's 2-stage studies and use
307  the code to verify the design in (2.1).
308  ********************************************************;
309
310  data sim2;
311      call streaminit(730317945);
312
313      type1 = 0;
314      power = 0;
315
316      do rep=1 to 5000;
317          null = rand('Binom', .3, 5);
318          alt = rand('Binom', .6, 5);
319
320          if null <= 1 then null=null;
321              else null = null+rand('Binom', .3, 9);
322          if alt <= 1 then alt=alt;
323              else alt = alt+rand('Binom', .6, 9);
324          if null>6 then type1=type1+(1/5000);
325          if alt>6 then power=power+(1/5000);
326      end;
327  run;
328
329  proc print data=sim2;
330      title 'Type I Error and Power of 2-stage simulation';
331      var type1 power;
332  run;
```

Relevant SAS Output:

Type I Error and Power of 2-stage simulation

Obs	type1	power
1	0.0824	0.798