

# Sample Size Calculation and Timeline Estimate for Progression-Free Survival

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## ABSTRACT

Progression-free survival (PFS) is frequently used as the primary endpoint in phase II and III studies for late-stage diseases in oncology. PFS is the duration from enrollment to disease progression or death, whichever occurs first. The actual occurrence of disease progression cannot be observed until the next scheduled assessment (interval censoring) or when death occurs before progression. The log-rank test is commonly used in the comparison of treatment effect on PFS. The sample size for PFS without adjusting for interval-censoring or taking into account the hazard ratio of survival is very likely to underachieve the desired power. Unfortunately, major software for sample size calculation (e.g., nQuery Advisor®, SAS®, PASS, and East®) does not have this function. The SAS macro demonstrated in this paper is focused on this unmet need and provides timeline estimate.

Key words: survival analysis, progression-free survival, staggered enrollment, power simulation, timeline projection.

## INTRODUCTION

Progression-free survival (PFS) is frequently used as the primary endpoint in phase II and III studies for late-stage diseases in oncology. PFS is the duration from enrollment to disease progression or death, whichever occurs first. The actual occurrence of disease progression cannot be observed until the next scheduled assessment (interval censoring) or when death occurs before progression. For example, if the actual (unknown) time of disease progression occurs at 4.2 and 5.6 months for patients A and B, respectively, and assume that the assessment is done every other month, the observed PFS is 6 months for both patients.

The log-rank test is commonly used in the comparison of treatment effect on PFS. The sample size for PFS based on the log-rank test without adjusting for interval-censoring or taking into account the hazard ratio of survival is very likely to underachieve the desired power. Unfortunately, major software for sample size calculation (e.g., nQuery Advisor, SAS, PASS, and East) does not have this function. Since the number of events determines the power of a logrank test, in a regulatory environment, the data cut-off date for the analysis should be specified by the number of events to be included in the analysis. Given the number of patients to be enrolled and the number of events to be observed, the SAS macro demonstrated in this paper takes into account interval censoring and the distributions of both TTP and survival in the power simulation for PFS. This macro also estimates when the pre-specified number of events will occur. In addition to PFS, which is the mixture of continuous and interval-censored data, we show how to extend the application of this macro to continuous endpoint and interval-censored endpoint.

## THE ALGORITHM OF THE MACRO

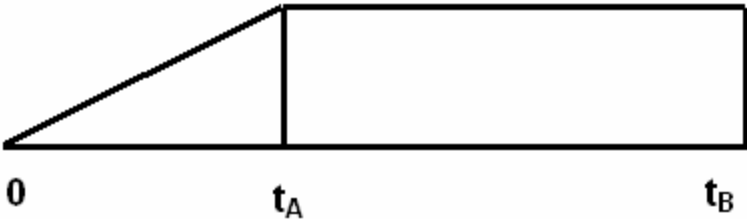
Several comments are inserted in the macro in the Appendix. Due to space constrain, only important and more complex code in the macro is illustrated in this section. The macro includes 4 major steps as follows:

1. Generate the data for all the number of trials specified in the simulation, including enrollment time, survival, actual and observed TTP, and PFS.
2. Determine when the pre-specified number of events will occur in each trial and determine if an observation is censored.
3. Use the SAS LIFETEST procedure and ODS to calculate and output the observed medians of PFS and the logrank p-value of each trial.
4. Estimate the power and project the timeline from the results obtained in the previous step.

## SIMULATION OF STAGGERED ENROLLMENT

The enrollment rate in clinical trials usually goes through a ramp like period when the sites are being initiated (the interval  $[0, t_A]$  in Figure 1). The enrollment rate is then stabilized (the interval  $(t_A, t_B]$  in Figure 1).

**Figure 1. Enrollment With a Ramp-Up Period [0, t<sub>A</sub>] and a Steady Accrual Period (t<sub>A</sub>, t<sub>B</sub>]**



Suppose it takes *a* months to complete the ramp-up period, during which the enrollment rate is linearly increasing. Also assume that the enrollment rate is *b* patients per month during the steady accrual period. If *n* patients will be enrolled, we have the following results:

- The number of patients enrolled during the ramp-up period =  $ab/2$ ,
- The duration of the steady accrual period in months =  $(n - ab/2)/b = n/b - a/2$ , and
- The total enrollment period in months =  $n/b + a/2$ .

From the results above, the probability for a patient to be enrolled during the ramp-up period and the steady accrual period is  $p_1 = (ab/2)/n$  and  $(1 - p_1)$ , respectively. The enrollment rate at time *t* is  $bt/a$ . Thus the distribution function of the enrollment time *t* during the ramp-up period is

$$F(t) = [t(bt/a)/2]/(ab/2) = (t/a)^2, \tag{1}$$

for any *t* in [0, *a*]. Since *F(t)* follows a uniform distribution on [0, 1], the random variable

$$T = a (U)^{1/2}, \tag{2}$$

where *U* follows a uniform distribution on [0, 1], can be used to simulate the enrollment time for patients enrolled during the ramp-up period.

For patients enrolled during the steady accrual period, the enrollment time *t* can be simulated by:

$$T = a + (n/b - a/2)U, \tag{3}$$

where *U* follows a uniform distribution on [0, 1]. In general, the enrollment time of any patient can be expressed as:

$$T = p_1 a (U)^{1/2} + (1 - p_1)[a + (n/b - a/2)U].$$

A two-step process is used to simulate the enrollment time of each patient. A uniform random variable on [0, 1] is first generated. If the value is less than or equal to  $p_1 = (ab/2)/n$ , the patient is enrolled during the ramp-up period and equation (2) is used to simulate the enrollment time; otherwise equation (3) is used to generate the enrollment time.

**SIMULATION OF THE OBSERVED PFS**

The exponential distribution is used to simulate the actual event time for TTP and survival. The simulated actual PFS is the minimum of these two values. Let *x* be the median time to event for the control arm and the hazard ratio of the control arm versus the experimental arm be *h*, where  $h > 1$ . Then the mean of the control arm is  $x/\log(2)$ , where  $\log(\cdot)$  is the natural logarithmic function. For exponential distributions, the percent improvement in median time to event is equal to  $100 \times (h - 1)\%$ . So the median and mean of the experimental arm are  $hx$ , and  $hx/\log(2)$ , respectively.

The SAS function *ranexp(x)* generates the exponential random variable with parameter 1 using the randomization seed in the parentheses. It is straightforward to show that for any non-negative *y*,  $y[\text{ranexp}(x)]$  generates an exponential random variable with mean *y*. This property is utilized to generate TTP and survival.

The simulation of the observed PFS is derived from the minimum of the simulated survival and the simulated observed TTP. The simulation of survival and actual TTP follows the method discussed earlier. The observed TTP can be simulated using:

$$\text{ObservedTTP} = \text{Ceil}\left(\frac{\text{ActualTTP}}{\text{AssessmentInterval}}\right) \cdot (\text{AssessmentInterval}), \quad (4)$$

where  $\text{Ceil}(x)$  is the minimum integer greater than or equal to the argument. For example, if the actual disease progression occurs 4.5 months after enrollment and the assessment is done every 2 months, then the observed TTP is  $\text{Ceil}(4.5/2) \times 2 = 3 \times 2 = 6$  (months). The calendar time of PFS is PFS plus the enrollment time.

## POWER SIMULATION

The data is sorted by the calendar time of PFS in each trial and the calendar time to observe the pre-specified number of events is determined. Patients enrolled after this time point are eliminated in each trial. For the remaining patients, the PFS observed after this cut-off time is censored at the cut-off time. The resulting data is used to calculate the two-sided logrank p-value and the observed median PFS for each trial using the LIFETEST Procedure. The estimated power is the proportion of the number of trials with p-values less than or equal to the significance level.

Let  $X_i$  be the random variable with value 1 if the result of the  $i$ -th trial is significant; otherwise 0.  $X_i$  follows a Bernoulli distribution with parameter  $p$ , where  $p$  is the power to be simulated. The estimated power is:

$$\hat{P} = \frac{\sum_{i=1}^n X_i}{n}, \quad (5)$$

where  $n$  is the total number of trials. Since  $\sum X_i$  follows a binomial distribution with parameters  $(n, p)$ ,  $\hat{P}$  has mean equal to  $p$  and variance equal to  $p(1-p)/n$ , which is less than or equal to  $1/(4n)$ . Using the normal approximation, the estimated 95% confidence interval for  $\hat{P}$  is:

$$\left( \max\left(0, \hat{P} - \frac{1.96}{\sqrt{4n}}\right), \min\left(1, \hat{P} + \frac{1.96}{\sqrt{4n}}\right) \right). \quad (6)$$

Note that the confidence interval above is conservative. If a large number of trials is used in the simulation,  $\sqrt{4n}$  in (6) can be replaced with  $\sqrt{n/[\hat{p}(1-\hat{p})]}$ .

## EXAMPLES

### EXAMPLE 1

The macro also generates the number of required events for continuous data using Schoenfeld's (1982) formula. Use the number of events from Schoenfeld's formula, this example validates if the power simulated by the macro for continuous data produces the expected power. This example also shows how to apply the macro to continuous data. The macro is run with 50% improvement (hazard ratio = 1.5) in TTP, one-to-one randomization, 90% power, and a two-sided significance level of 0.05. The number of required event is 256 using Schoenfeld's formula. In order to verify if this number of events will achieve 90% power through the macro, we also use 256 patients with 0 dropout rate. In other words, all the patients will be followed until progression.

A small number (0.0001) is assigned to the assessment interval so that the observed TTP becomes continuous. Two large numbers are assigned to the median overall survival of the control and experimental arms such that the simulated PFS is identical to the continuous TTP. Using 2000 trials, the estimated power and 95% confidence interval are 0.897 and (0.875, 0.919), respectively. With median TTP equal to 10, the average time to reach 256 events is quite long (128.42) and the confidence interval is wide (97.58, 186.19). This is due to the long tail of the exponential distributions. The SAS output is not displayed due to space constrain.

## EXAMPLE 2

Suppose a clinical trial is to be designed to detect a difference in PFS, in which the median of TTP is 14 months versus 20 months and the median of survival is 56 months versus 62 months. Disease progression is assessed every 12 weeks (2.76 months). If TTP is used to calculate the sample size without considering survival, the number of required events to reach an 80% power without adjustment for interval censoring is 247. After adjusting for interval censoring and taking survival into account, the number of events required is about 390, a 58% increase from 247! The output of the macro is listed below.

```
POWER SIMULATION AND TIMELINE ESTIMATE FOR PROGRESSION-FREE SURVIVAL 1

SIMULATION RESULTS VALUE
-----
INPUT

NUMBER OF SIMULATIONS 2000
RANDOMIZATION SEED 39846
RAMP-UP PERIOD (TIME TO ALL SITES INITIATED) 6
STEADY RECRUIT PERIOD 18
RANDOMIZATION RATIO--(CONTROL SIZE)/(TOTAL SAMPLE SIZE) 0.5
DROPOUT RATE (CONTROL, EXPERIMENT) 0, 0
TOTAL NUMBER OF PATIENTS ENROLLED 595
TOTAL NUMBER OF EVENTS TO BE OBSERVED 390
MEDIAN TTP--CONTROL ARM 14
HAZARD RATIO FOR TTP (CONTROL VS. EXPERIMENT) 1.429
MEDIAN SURVIVAL--CONTROL ARM 56
MEDIAN SURVIVAL--EXPERIMENTAL ARM 62
TYPE I ERROR FOR TWO-SIDED TEST 0.05
INTENDED POWER 0.80
ASSESSMENT INTERVAL FOR DISEASE PROGRESSION 2.76

OUTPUT

NUMBER OF PATIENTS PER MONTH AT FULL ENROLLMENT 28.3
OBSERVED MEDIAN PFS--CONTROL ARM (95% CI) 11.57 (11.04, 13.8)
OBSERVED MEDIAN PFS--EXPERIMENTAL ARM (95% CI) 16.61 (13.8, 19.32)
TIME TO THE ANALYSIS (95% CI) 35.44 (33.78, 37.24)
SIMULATED POWER (95% CI) 0.810 (0.788, 0.832)
NUMBER OF EVENTS REQUIRED FOR CONTINUOUS DATA 247
```

## CONCLUSION

The SAS macro demonstrated in this paper is designed with both clinical operation and statistics in mind. With the ramp-up period, total enrollment period, and full enrollment rate per month, clinical operation personnel can plan how many sites to be initiated and when to complete site initiation. Alternatively, clinical operation personnel can provide the maximum enrollment rate and time to initiate all sites. The project statistician can then calculate the total enrollment period and project when the final analysis will occur using this macro. Since the enrollment rate is assumed linearly increasing from 0, a nonlinear enrollment curve should be adjusted in order to reach a precise projection. The beginning of the ramp-up period should be the month when the first patient is enrolled, and the end point of the ramp-up period should be the month when enrollment rate is stabilized. For example, if the first site of a clinical trial is initiated in January, the first patient is enrolled in February, all the sites are initiated in June, and this trial is not well-known to the public until September in the same year, then the beginning and end points of the ramp-up period should be February and September, respectively.

The required events for TTP or PFS and the sample size can be approximated with try and error using a smaller number of trials for simulation, e.g., 500, until the estimated power is close to the desired power. Given any medians and hazard ratio, you can first run the macro with one trial to obtain the number of events needed for continuous data. Then double and triple this number as the required number of events and sample size, respectively. Fine tune the sample size and number of events until the estimated power is close to the intended power. The number of trials required to reach the desired precision for the power simulation can be derived from equation (6).

FDA has pointed out that several phase 3 clinical trials were underpowered. The results in Example 2 echoes FDA's statement. In planning a clinical study using PFS as the primary endpoint, it is important to take interval censoring and survival into account. This is due to the following reasons:

1. The actual event time of progression cannot be observed until the next scheduled assessment. Thus patients with different actual TTP may have the same observed TTP.
2. Although the median survival is usually much longer than that of TTP, a substantial amount of PFS events may be caused by death. Assuming an exponential distribution for the actual TTP and survival with median  $\lambda_1$  and  $\lambda_2$ , respectively, it is straightforward to show that the probability of deaths occurring before progression is  $\lambda_1/(\lambda_1 + \lambda_2)$ . In Example 2, this probability is 20% and 24% for the control and experimental arms, respectively.
3. If a drug is efficacious, it has been shown in clinical studies that the improvement in survival is close to the extended TTP or PFS. See Rai, et al (2000) and Petrylak (2004). In other words, the survival improvement in terms of hazard ratio will be much smaller than that of TTP.

The macro presented in this paper addresses the three issues above. Although the exponential distribution is used to model TTP and survival, this macro can easily be extended to Weibull or other survival distributions.

## APPENDIX: THE SOURCE CODE OF THE SAS MACRO

```

1  * program name: Power simulation for PFS.sas;
2  * Author: Chung-Kuei Chang;
3  * purpose: Estimate the power and timing given # of patients and required events
4  *           Assume a specified pattern of enrollment:
5  *           First a ramp-like accrual rate during time 'ramp',
6  *           then a steady accrual rate during time 'steady';
7  *           Simulation results: Time to observe the prespecified # of events,
8  *           The estimated power based on observed PFS is therefore adjusted for
8  ! interval censoring.
9  * Output: Observed median PFS, time to analysis, power, and required number of
9  ! events from the formula by Schoenfeld, 1981;
10
11
12  dm 'lst;clear;log;clear';
13  options ls=78 ps=54 pageno=1 notes mprint nosymbolgen;
14  title "POWER SIMULATION AND TIMELINE ESTIMATE FOR PROGRESSION-FREE
14  ! SURVIVAL";
15  footnote;
16
17  %macro simul(
18  ntrial=2000,           /* # of trials in the simulation */
19  seed=0,               /* Seed for randomization */
20  ramp=5,               /* Time from studt start to reaching full
20  ! enrollment rate or to all sites initiated */
21  steady=19,           /* Duration of steady accrual */
22  totalpat=684,        /* Total # of patients enrolled */
23  r0_rand=0.5,         /* Randomization ratio = (control
23  ! size)/(total sample size) */
24  eventsFL=637,        /* # of events to be observed at the analysis */
25  medttp0=4.0,         /* Median time to event of the control group */
26  hr=1.3,              /* Hazard ratio (Control group/Experiment
26  ! group) */
27  ttpases=0.23,        /* Assessment interval for event (progression) */
28  alphafin=0.05,       /* Type I error */
29  intpower=0.90,       /* The intended power */
30  medos0=6,            /* Median survival for the control */
31  medos1=7.2,          /* Median survival for the treated */
32  DOutRate0=0,         /* Drop-out rate for the control group */
33  DOutRate1=0,         /* Drop-out rate for the experiment group */
34  );
35
36  proc datasets kill;
37  run;
38

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39  *** # of events required for the power from formula;
40  data null;
41  r=&r0_rand;
42  zalpha_2=probit(1-&AlphaFin/2);
43  zbeta=probit(&intpower);
44  delta=&hr;
45  *nevent=ceil((1+r)**2*(zalpha_2+zbeta)**2/(r*(log(delta))**2));
46  nevent=ceil((zalpha_2+zbeta)**2/(r*(1-r)*(log(delta))**2));
47  call symput("nevent", trim(left(nevent)));
48  run;
49
50  *** Create the simulation data;
51
52  data datsimul;
53      * Group size in the two treatment arms;
54      size0=round(&totalpat*&r0_rand, 1);
55      size1=&totalpat-size0;
56
57      * Total enrollment period--ramp-up period + steady-accrual period
57 ! ;
58      totaccr = &ramp + &steady;
59
60      * Probability that a patient will be enrolled during the ramp-up
60 ! period;
61      p1=0.5*&ramp/(0.5*&ramp + &steady);
62
63      * Probability that a patient will be enrolled during the steady
63 ! accrual phase;
64      p2=1-p1;
65
66      call symput("accrate", &totalpat/(0.5*&ramp+&steady));
67
68      *** Calculate the median TTP of the experiment group.;
69      medttp1=&medttp0*&hr;
70      call symput("medttp1", trim(left(medttp1)));
71
72      *** Assessment interval for disease progression;
73      ttpases=&ttpases;
74
75      * Create simulation data for each trial;
76      do trial=1 to &ntrial;
77      * Loop over groups;
78      do group=0 to 1;
79          if group=0 then
80              do;
81                  size      = size0;
82                  meanttp  = &medttp0/log(2);
83                  meanos   = &medOS0/log(2);
84                  doutrate=&DOutRate0; * Dropout rate;
85              end;
86          else if group=1 then
87              do;
88                  size      = size1;
89                  meanttp  = medttp1/log(2);
90                  meanos   = &medOS1/log(2);
91                  doutrate=&DOutRate1; * Dropout rate;
92              end;
93          * Loop over patients in the given group;
94          do mm=1 to size;
95          * Determine if the patient comes in during the
95 ! ramp phase or later;
96              if ranuni(&seed)<=p1 then
97                  enrftime =

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97 ! &ramp*(ranuni(&seed)**0.5;
98
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else
    enrlltime = &ramp +
        * TTP of the patient;
    ttp = ranexp(&seed)*meanttp;
    if doutrate=0 or (doutrate>0 and
do;
    if ttpases>0 then ttpobs =
    else ttpobs=ttp; * Observed TTP;
    dropout=0; * Indicator for
non-dropout patients;
end;
else
do; *** Dropout patients;
    * Assume that the dropout patients do
not receive treatment benefit;
    if group=1 then ttp =
    ranexp(&seed)*&medttp0/log(2); * Actual TTP;
    if ttpases>0 then ttpobs =
    floor(ranuni(&seed)*ttp/ttpases)*ttpases; * Observed TTP;
    else if ttpases=0 then
    ttpobs=ranuni(&seed)*ttp; * Observed TTP;
    dropout=1; * Indicator for
dropout patients;
end;
OS=meanos*ranexp(&seed);*** Survival time
* Assume that the dropout patients do not
receive treatment benefit;
if dropout=1 and group=1 then
OS=&medOS0/log(2)*ranexp(&seed);
PFSobs = enrlltime + min(ttpobs, OS);
PFStime = min(ttpobs, OS);
output datsimul;
end; * For mm;
end; * For Group;
end; * For trial;
run;
*** Estimate when the analysis will occur.;
proc sort data=datstimul;
by trial pfsobs;
run;
data timefin;
set datstimul;
by trial pfsobs;
retain pfsevent 0;
if first.trial then pfsevent=0;
if dropout=0 then pfsevent+1;
if pfsevent=round(&eventsFL, 1);
timefin=pfsobs;
keep trial timefin;
run;
*** Estimate when the event number = prespecified # of events
(&eventsFL), i.e., time of the analysis.;
proc univariate data=timefin noprint;

```

```

146         var timefin;
147         output out=timeFL median=median p5=p5timefl p95=p95timefl;
148 run;
149
150 data _null_;
151     set timeFL;
152     call symput( "timeFL", trim(left(round(median, 0.01))));
153     call symput( "p5timeFL", trim(left(round(p5timeFL, 0.01))));
154     call symput( "p95timeFL", trim(left(round(p95timeFL, 0.01))));
155 run;
156
157 *** create final pfs analysis data set;
158 data setFL;
159     merge datsimul timefin;
160     by trial;
161     if enrtime <= timefin; *** Exclude patients enrolled after the
161! time of the analysis.;
162     if pfsobs>timefin then
163     do;
164         censor=1; *** Censored observation;
165         pfstime=timefin-enrtime;*** Censored at cut-off date;
166     end;
167     else censor=0; *** Event;
168     if dropout=1 then censor=1; *** All dropout patients are censored
168! ;
169 run;
170
171 *** Calculate median observed pfs and logrank test results;
172 ODS LISTING CLOSE;
173 ODS OUTPUT QUARTILES=QUARTILES;
174 ODS OUTPUT HOMTESTS=HOMTESTS;
175
176 proc lifetest data=setFL;
177     by trial;
178     STRATA GROUP;
179     time pfstime*censor(1);
180 run;
181
182 ODS LISTING;
183
184 *** Gest observed median PFS;
185 proc sort data=quartiles;
186     where (percent=50);
187     by group;
188 run;
189
190 proc univariate data=quartiles noprint;
191     by group;
192     var estimate;
193 output out=temp2 median=median p5=p5 p95=p95;
194 run;
195
196 * observed pfs values (pfsobs) in the simulation data set;
197 data _null_;
198     set temp2;
199     median=round(median, 0.01);
200     p5=round(p5, 0.01);
201     p95=round(p95, 0.01);
202     if group=0 then
203     do;
204         call symput("obpfs0FL", trim(left(median)));
205         call symput("p5_0", trim(left(p5)));
206         call symput("p95_0", trim(left(p95)));

```



```

207         end;
208         else
209             if group=1 then
210                 do;
211                     call symput("obpfs1FL", trim(left(median)));
212                     call symput("p5_1", trim(left(p5)));
213                     call symput("p95_1", trim(left(p95)));
214                     end;
215 run;
216
217 *** Gest the logrank test results;
218 data final;
219     set homtests end=eof;
220     retain power 0;
221     where upcase(test)="LOG-RANK";
222     if .<probchisq <= &alphafin then power+1;
223     if eof then
224         do;
225         power=round(power/&ntrial, 0.001);
226             low_95CI=round(max(0, power-1.96/sqrt(4*&ntrial)), 0.001)
226! ;
227             high_95CI=round(min(power+1.96/sqrt(4*&ntrial), 1),
227! 0.001);
228             call symput("powerFL", trim(left(power)));
229             call symput("p5power", trim(left(low_95ci)));
230             call symput("p95power", trim(left(high_95ci)));
231             full_enroll=&totalpat/(&ramp/2+&steady);
232             call symput("full", compress(round(full_enroll,0.1)));
233             output;
234         end;
235 run;
236
237 data output;
238     length result $120. value $30.;
239     result="INPUT"; value="";OUTPUT;
240     RESULT=""; value=""; output;
241     RESULT="NUMBER OF SIMULATIONS"; value="&NTRIAL";OUTPUT;
242     RESULT="RANDOMIZATION SEED"; value="&SEED";OUTPUT;
243     RESULT="RAMP-UP PERIOD (TIME TO ALL SITES INITIATED)"; value="&RAMP";
243! OUTPUT;
244     RESULT="STEADY RECRUIT PERIOD"; value="&STEADY";OUTPUT;
245     RESULT="RANDOMIZATION RATIO--(CONTROL SIZE)/(TOTAL SAMPLE SIZE)";
245! value="&R0_RAND";OUTPUT;
246     RESULT="DROPOUT RATE (CONTROL, EXPERIMENT)"; value="&DOUtrate0.,
246! &DOUtrate1";OUTPUT;
247     RESULT="TOTAL NUMBER OF PATIENTS ENROLLED"; value="&TOTALPAT";OUTPUT;
248     RESULT="TOTAL NUMBER OF EVENTS TO BE OBSERVED"; value="&EVENTSFL";OUTPUT
248! ;
249     RESULT="MEDIAN TTP--CONTROL ARM"; value="&MEDTTP0";OUTPUT;
250     RESULT="HAZARD RATIO FOR TTP (CONTROL VS. EXPERIMENT)"; value="&HR";
250! OUTPUT;
251     RESULT="MEDIAN SURVIVAL--CONTROL ARM"; value="&MEDOS0";OUTPUT;
252     RESULT="MEDIAN SURVIVAL--EXPERIMENTAL ARM"; value="&MEDOS1";OUTPUT;
253     RESULT="TYPE I ERROR FOR TWO-SIDED TEST"; value="&ALPHAFIN";OUTPUT;
254     RESULT="INTENDED POWER"; value="&INTPOWER";OUTPUT;
255     RESULT="ASSESSMENT INTERVAL FOR DISEASE PROGRESSION"; value="&TTPASES";
255! OUTPUT;
256     RESULT=""; value=""; OUTPUT;OUTPUT;
257     RESULT="OUTPUT"; value="";OUTPUT;
258     RESULT=""; value=""; OUTPUT;
259     RESULT="NUMBER OF PATIENTS PER MONTH AT FULL ENROLLMENT"; value="&FULL";
259! OUTPUT;
260     RESULT="OBSERVED MEDIAN PFS--CONTROL ARM (95% CI)"; value="&OBPFS0FL

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```

260! (&p5_0, &p95_0)";OUTPUT;
261  RESULT="OBSERVED MEDIAN PFS--EXPERIMENTAL ARM (95% CI)";
261! value="&OBPFS1FL (&p5_1, &p95_1)";OUTPUT;
262  RESULT="TIME TO THE ANALYSIS (95% CI)"; value="&TIMEFL (&p5timefl,
262! &p95timefl)";OUTPUT;
263  RESULT="SIMULATED POWER (95% CI)"; value="&POWERFL (&p5power,
263! &p95power)";OUTPUT;
264  RESULT="NUMBER OF EVENTS REQUIRED FOR CONTINUOUS DATA"; value="&NEVENT";
264! OUTPUT;
265  proc print data=output label split="*" noobs;
266    label RESULT="SIMULATION RESULTS*-----"
267    value="VALUE*-----";
268  run;
269
270  %mend simul;

```

Example:

```

%simul(ntrial=2000, seed=0, ramp=6, steady=18, totalpat=595, r0_rand=0.5,
eventsFL=395, medttp0=14, hr=1.429, ttpases=2.769, alphafin=0.05, intpower=0.80,
medOS0=56, medOS1=62, DOutRate0=0, DOutRate1=0);

```

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## ACKNOWLEDGEMENT

I would like to thank Dr. Christian Kappeler for his helpful comments during the development of this macro.

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