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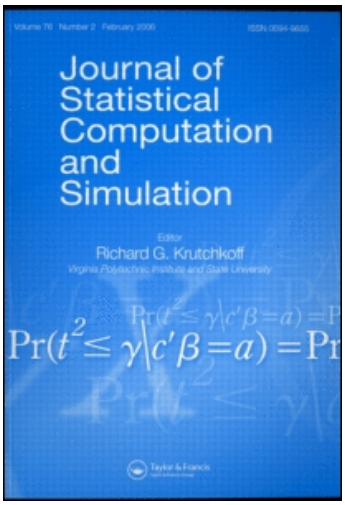

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Sample size and power determination for stratified clinical trials

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Sample Size and Power Determination for Stratified Clinical Trials

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This paper presents an ISO FORTRAN subroutine for determining the required sample size or power in a stratified clinical trial. The algorithm permits a post-accrual follow up period, censored observations, patient strata or risk groups, and unequal case allocation schemes. An example which illustrates use of the subroutine is provided.

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1. INTRODUCTION

The planning of a comparative clinical trial for survival time must account for certain conditions not encountered in the usual types of statistical experiments. First of all, patients are accrued into the trial sequentially rather than all at once. Secondly, there is usually a period of post-accrual observation or follow-up during which no new cases are entered. As a result, some survival time observations will be incomplete or right censored simply because the corresponding patients have not yet failed by the time the data are analyzed. Additional complexities arise from the fact that (i) clinical trials are usually "stratified" in order to balance treatments over two or more risk groups and (ii) treatment assignment procedures are not always based on an equal-allocation scheme.

The purpose of this paper is to provide an ISO Fortran subroutine for use in determining the required sample sizes for comparative clinical trials having the aforementioned properties. The subroutine can also be used to determine the statistical power corresponding to a particular sample size. It is assumed that cases are accrued into the trial uniformly over time and that the survival time distribution for a particular stratum and treatment is the 1-parameter exponential. While the exponential assumption is surely

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not valid in all circumstances, it is still useful for providing a general idea of the accrual needs of a given study.

Section 2 reviews the theory underlying the calculations. Section 3 describes the subroutine and supplies a sample driver program and an example.

We note that George and Desu (1974) give tables for sample size for the special case where there is no post-accrual follow-up period, a single stratum, and an equal allocation of patients to the control and experimental groups.

2. RESULTS

Suppose that accrual into the trial begins at chronologic time 0 and continues for T time units. Thereafter, patients are followed for τ additional time units, until chronologic time $T+\tau$. Those who have not failed by time $T+\tau$ will have censored survival times. Suppose that patients enter the trial according to a uniform distribution over $(0, T)$ and let N denote the expected number of cases that enter per unit time.

Each patient is initially classified into one of K risk groups, or strata. Within each stratum, the patients are assigned to the control (C) or experimental (E) treatment in proportions θ and $1-\theta$, respectively. If p_j denotes the expected proportion of patients in stratum j, the total expected numbers of control and experimental patients in stratum j are

$$N_C^{(j)} = NTp_j\theta$$

and

$$N_E^{(j)} = NTp_j(1-\theta).$$

Within stratum j, the survival time distributions for the control and experimental groups are exponential with rate parameters $\lambda_C^{(j)}$ and $\lambda_E^{(j)}$. Moreover, it is assumed that the ratio $\Delta = \lambda_C^{(j)}/\lambda_E^{(j)}$ is constant over strata. Thus, while the survival time distribution may vary over strata, the relative effect of experimental to control therapy is the same for each.

Let $r_C^{(j)}$ and $r_E^{(j)}$ denote the number of observed failures in the control and experimental groups within stratum j, and let $V_C^{(j)}$ and $V_E^{(j)}$ be the corresponding total observed time, or uptime. Then

$$\hat{\lambda}_C^{(j)} = r_C^{(j)}/V_C^{(j)}$$

and

$$\hat{\lambda}_E^{(j)} = r_E^{(j)}/V_E^{(j)}$$

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are the maximum likelihood estimators of $\lambda_C^{(j)}$ and $\lambda_E^{(j)}$ and the usual test for

$$H_0: \Delta = 1 \text{ vs. } H_A: \Delta > 1$$

is based on the asymptotic distribution of

$$Q = \sum_{j=1}^{K} w_j Q_j, \tag{2.1}$$

where

$$Q_j = ln(\hat{\lambda}_C^{(j)} / \hat{\lambda}_E^{(j)})$$

and the w_j are weights. Since Q_j is asymptotically normal with mean $\ln(\Delta)$ and variance

$$\sigma_j^2 = \frac{1}{E(r_C^{(j)})} + \frac{1}{E(r_E^{(j)})},$$

the w_j which yield $E(Q) = \ln(\Delta)$ and minimize the variance of Q are easily shown to be

$$w_j = \frac{1}{\sigma_j^2 \sum_{j=1}^{K} \frac{1}{\sigma_j^2}}.$$

The corresponding minimized variance of Q is

$$V(\Delta) = \Sigma w_j^2 \sigma_j^2 = \frac{1}{\Sigma \frac{1}{\sigma_j^2}} \tag{2.2}$$

Suppose $\pi_C^{(j)}$ denotes the probability that a control-group patient in stratum j fails by chronologic time $T + \tau$, and let $\pi_E^{(j)}$ be defined similarly. It follows that $E(r_C^{(j)}) = N_C^{(j)} \pi_C^{(j)}$ and $E(r_E^{(j)}) = N_E^{(j)} \pi_E^{(j)}$ and so (2.2) becomes

$$V(\Delta) = [NT(\theta)(1-\theta)\gamma(\Delta)]^{-1} \tag{2.3}$$

where

$$\gamma(\Delta) = \sum_{j=1}^{K} \frac{p_j \pi_C^{(j)} \pi_E^{(j)}}{\theta \pi_C^{(j)} + (1-\theta)\pi_E^{(j)}}.$$

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Hence the 1-sided level α test for H_0 based on Q and its asymptotic distribution is that which rejects whenever

$$Q > \sqrt{V(1)} \cdot \Phi^{-1}(1-\alpha) = C, \tag{2.4}$$

where $\Phi(x)$ is the probability that a standard normal random variable does not exceed x and Φ^{-1} is the inverse function. The power of this test against the alternative $\Delta = \Delta_A > 1$ is

$$\beta(\Delta_A) = 1 - \Phi\left(\frac{C - \ln \Delta_A}{\sqrt{V(\Delta_A)}}\right). \tag{2.5}$$

Alternatively, the necessary accrual per unit time, N, to achieve power $\beta(\Delta_A)$ is

$$N = \frac{[\gamma^{-1/2}(1)\Phi^{-1}(1-\alpha) - \gamma^{-1/2}(\Delta)\Phi^{-1}(1-\beta)]^2}{T\theta(1-\theta)\ln^2(\Delta)}. \tag{2.6}$$

Since accrual into the trial is uniform over $(0, T)$, it is seen that

$$\begin{aligned}\Pi_c^{(j)} &= \int_0^T \frac{1}{T}\{1 - \exp[-\lambda_c^{(j)}(T + \tau - t)]\}dt \\ &= 1 - \exp[-\lambda_c^{(j)}\tau] \cdot \{1 - \exp[-\lambda_c^{(j)}T]\}/(\lambda_c^{(j)}T).\end{aligned}$$

Similarly,

$$\Pi_E^{(j)} = 1 - \frac{\exp(-\lambda_E^{(j)}\tau)}{\lambda_e^{(j)}T}[1 - \exp(-\lambda_e^{(j)}T)].$$

Thus, one can first solve for $\Pi_c^{(j)}$ and $\Pi_E^{(j)}$ and then use (2.5) or (2.6) to determine $\beta(\Delta_A)$ or N.

3. SUBROUTINE, EXAMPLE

The subroutine calling sequence and formal parameter description are as follows:

SUBROUTINE POWER (*T*, TAU, *N*, THETA, DELTA, ALPHA, NS, CLAM, PROP, INDIC, CPIE, EPIE, BETA, IFAULT)

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Foramal Parameters

T	Real	input:	length of accrual period
TAU	Real	input:	length of follow-up period
N	Integer	input:	accrual rate per unit time (if INDIC $=0$)
		output:	required accrual rate (if INDIC $=1$)
THETA	Real	input:	proportion of patients allocated to control group.
DELTA	Real	input:	ratio of control hazard rate to experimental hazard rate at which power is evaluated.
ALPHA	Real	input:	Type I error
NS	Integer	input:	number of strata
CLAM	Real array (NS)	input:	CLAM(J) is hazard rate for control patients in stratum J.
PROP	Real array (NS)	input:	PROP(J) is the proportion of cases in stratum J.
INDIC	Integer	input:	INDIC $=0$ if N is inputted and INDIC $=1$ if BETA is inputted.
CPIE	Real array (NS)	output:	CPIE(J) is the probability that a control patient in stratum J is observed to fail.
EPIE	Real array (NS)	output:	EPIE(J) is the probability that an experimental patient on stratum J is observed to fail.
BETA	Real	input:	desired power (if INDIC $=1$)
		output:	power (if INDIC $=0$)
IFAULT	Integer	output:	error indicator; equal to

0 if no error
1 if $T \leqq 0.0$
2 if TAU < 0.0
3 if CLAM(J) $\leqq 0.0$ for some J
4 if DELTA $\leqq 0.0$
5 if $N \leqq 0$
6 if ALPHA $\notin (0.0, 1.0)$
7 if NS $\leqq 0$
8 if PROP(J) $\leqq 0.0$ for some J
9 if $\sum_J$ PROP(J) $\neq 1.0$
10 if THETA $\notin (0.0, 1.0)$
11 if BETA $\notin (0.0, 1.0)$
12 if INDIC is not 0 or 1.

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Auxiliary Subroutines Called:

1. GAUINV – Alg. AS 70, *J. Roy. Statist. Soc., C* (1974) 23, 1.
2. ALNORM – Alg. AS 66, *J. Roy. Statist. Soc., C* (1973) 22, 3.

To illustrate the subroutine, consider the case $T=2$, TAU $=2$, THETA $=0.5$, DELTA $=1.5$, ALPHA $=0.05$, NS $=3$, CLAM $=(1, 0.8, 0.5)$, and PROP $=(0.4, 0.4, 0.2)$. This represents a trial with 2 years of accrual, two years of follow-up, and 3 strata or risk groups for which the control-group hazard rates are 1, 0.8 and 0.5. Suppose we wish to determine the power for the case when the accrual rate is $N=100$ cases per year. Then setting INDIC $=0$ yields a power of BETA $=0.847$ against the alternative $\Delta=1.5$. By examining the outputted values of CPIE and EPIE, we also see that the expected proportion of deaths in the 3 risk groups are (0.941, 0.899, 0.767) for the control group and (0.854, 0.788, 0.625) for the experimental group.

Conversely, suppose we wished to attain a power of 0.80 against the alternative $\Delta=1.5$. Then by setting INDIC $=1$ and BETA $=0.8$, the program indicates the necessary accrual rate to be $N=86$ cases per year.

Acknowledgments

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Reference

George, S. L. and Desu, M. M. (1974). Planning the size and duration of a clinical trial studying the time to some critical event. *Journal of Chronic Diseases* **27**, 15–24.

```
C SAMPLE DRIVER PROGRAM
  DIMENSION PROP(3), CLAM(3), CPIE(3), EPIE(3)
  CLAM(1)=1.0
  CLAM(2)=0.8
  CLAM(3)=0.5
  PROP(1)=0.4
  PROP(2)=0.4
  PROP(3)=0.2
  INDIC=0
  N=100
  CALL POWER(2.0, 2.0, N, 0.5, 1.5, 0.05, 3, CLAM, PROP, INDIC, CPIE, EPIE,
  +BETA, IFAULT)
```

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```
      PRINT 7, IFAULT
    7 FORMAT(1X, 7HIFAULT =, I2)
      PRINT 5, (CPIE(I), I = 1, 3)
    5 FORMAT(1X, 5HCPIE =, 3F9.5)
      PRINT 4, (EPIE(I), I = 1, 3)
    4 FORMAT(1X, 5HEPIE =, 3F9.5)
      PRINT 6, INDIC, N, BETA
    6 FORMAT(1X, 6HINDIC =, I2, /, 1X, 2HN =, I4, /, 1X, 5HBETA =, F8.5)

      INDIC = 1
      BETA = 0.8
      CALL POWER(2.0, 2.0, N, 0.5, 1.5, 0.05, 3, CLAM, PROP, INDIC, CPIE, EPIE,
     +BETA, IFAULT)

      PRINT 6, INDIC, N, BETA
      STOP
      END
```

OUTPUT:

```
      IFAULT = 0
      CPIE = 0.94149 0.89929 0.76746
      EPIE = 0.85441 0.78840 0.62527

      INDIC = 0
      N = 100
      BETA = 0.84727

      INDIC = 1
      N = 86
      BETA = 0.80000

      SUBROUTINE POWER(T, TAU, N, THETA, DELTA, ALPHA, NS, CLAM,
     +PROP, INDIC, CPIE, EPIE, BETA, IFAULT)

      DIMENSION PROP(NS), CLAM(NS), CPIE(NS), EPIE(NS)

      IFAULT = 0
      IF(T.LE.0.0)IFAULT = 1
      IF(TAU.LT.0.0)IFAULT = 2
      IF(DELTA.LE.0.0)IFAULT = 4
      IF(ALPHA.LT.0.0.OR.ALPHA.GT.1.0)IFAULT = 6
      IF(NS.LE.0)IFAULT = 7
      P = 0.0
      DO 1 I = 1, NS
      IF(CLAM(I).LE.0.0)IFAULT = 3
      IF(PROP(I).LE.0.0)IFAULT = 8
      P = P + PROP(I)
    1 CONTINUE
      IF(P.NE.1.0)IFAULT = 9
      IF(THETA.LE.0.0.OR.THETA.GE.1.0)IFAULT = 10
      IF(INDIC.NE.0.AND.INDIC.NE.1)IFAULT = 12
```

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```
      IF(INDIC.EQ.1)GO TO 4
      IF(N.LE.0)IFAULT=5
      GO TO 5
    4 IF(BETA.LE.0.0.OR.BETA.GE.1.0)IFAULT=11
    5 IF (IFAULT.NE.0)GO TO 3


      DO 2 I=1, NS
      ELAM=CLAM(I)/DELTA
      CPIE(I)=1.-(1./(T*CLAM(I)))*(EXP(-CLAM(I)*TAU)-EXP(-CLAM(I)*T
     +-CLAM(I)*TAU))
      EPIE(I)=1.-(1./(T*ELAM))*(EXP(-ELAM*TAU)-EXP(-ELAM*T
     +-ELAM*TAU))
    2 CONTINUE


C FIRST CALCULATED IS BETA GIVEN N.

      IF(INDIC.EQ.1) GO TO 7
      WN=0.0
      WA=0.0
      DO 8 I=1,NS
      FN=FLOAT(N)*PROP(I)*T
      FNC=FN*THETA
      FNE=FN-FNC
      VARNUL=(FNC+FNE)/(FNC*FNE*CPIE(I))
      VARALT=(1.0/(FNC*CPIE(I)))+(1.0/(FNE*EPIE(I)))
      WN=WN+1./VARNUL
      WA=WA+A./VARALT
    8 CONTINUE

      VN=1.0/WN
      VA=1.0/WA

C GAUINV FINDS PERCENTAGE POINTS OF THE
C NORMAL DISTRIBUTION
C ALGORITHM AS 70 APPL. STATIST.(1974) VOL.23, NO.1

      X=GAUINV(ALPHA, IFAUL)
      X=-X
      CRIT=X*SQRT(VN)
      Y=(CRIT-ALOG(DELTA))/SQRT(VA)

C ALNORM EVALUATES THE TAIL AREA OF THE STANDARD
C NORMAL CURVE
C ALGORITH AS 66 APPL. STATIST.(1973) VOL.22, NO.3

      BETA=ALNORM(T,.TRUE.)
      GO TO 3

C NEXT CALCULATED IS N GIVEN BETA.
```

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```
7 WNN=0.0
  WAN=0.0
  DO 9 I=1,NS
  F=PROP(I)*T
  FC=F*THETA
  FE=F-FC
  VARNUN=(FC+FE)/(FC*FE*CPIE(I))
  VARALN=(1./(FC*CPIE(I)))+(1./(FE*EPIE(I)))
  WNN=WNN+1./VARNUN
  WAN=WAN+1./VARALN
9 CONTINUE

  VNN=1./WNN
  VAN=1./WAN

  X=GAUINV(ALPHA, IFAUL)
  X=-X
  CRISRN=X*SQRT(VNN)
  T=1.0-BETA
  Y=GAUINV(T,IFAUL)
  SN=(CRISRN-Y*SQRT(VAN))/ALOG(DELTA)
  N=SN*SN+0.5
3 RETURN
  END
```

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