Introduction to Clinical trials

Instructor:
Constantin Yiannoutsos, Ph.D.
Professor of Biostatistics
Indiana University
School of R.M. Fairbanks School of Public Health, Department of Biostatistics

Power and sample size calculations

Principles

The following concepts will be referred to repeatedly in this lecture:

Power:	1-β
β level:	Type II error probability
α level:	Type I error probability
Likelihood ratio:	Relative strength of evidence
Sample size:	Number of experimental subjects
Effect size:	Treatment difference expressed as the number of standard deviations
Number of events:	Number of subjects with a specific outcome
Study duration:	Time from beginning of the trial to end of follow-up
Percent censoring:	Proportion of participants without an event by the end of the study
Allocation ratio:	Ratio of sample size in the treatment groups
Accrual rate:	New subjects entered per unit of time
Loss to follow-up rate:	Rate at which study participants are lost before outcomes are observed
Follow-up period:	Interval from end of accrual to end of study
Δ:	Smallest treatment effect of interest based on clinical considerations

Power

Power is the chance that a true difference will be detected by the study. There are a number of conceptual difficulties with this:

- Power is defined hypothetically (the treatment effect is actually present) as opposed to the null hypothesis of no effect or treatment difference
- Power is related to the experiment-wide (versus experimental-unit) variation
- Power cannot be separated by the sample size and the treatment effect. Thus, statements like "this study produced 90% power" are erroneous and possibly misleading. In fact *any* study can be made to generate any level of power (just assume a larger effect).

Early developmental trials
Translational studies

In translational trials, the sample size n is such that it would ensure that the absolute error lies below some threshold d with high probability. In other words,

$$\Pr(\left|\bar{X} - \mu\right| \leq d) \geq 1 - \alpha$$

which is equivalent to

$$\Pr\left(\frac{-d}{\sigma/\sqrt{n}} \leq \frac{\bar{X} - \mu}{\sigma/\sqrt{n}} \leq \frac{d}{\sigma/\sqrt{n}}\right) \geq 1 - \alpha$$

thus,

$$z_{1-\alpha/2} \leq \frac{d}{\sigma/\sqrt{n}}$$

so the required sample size n is

$$n = \left(z_{1-\alpha/2}\frac{\sigma}{d}\right)^2$$

Early developmental trials
Translational studies (continued)

The above can be expressed in terms of *effect size*. That is, we may want to calculate the sample size required to ensure (at the $\alpha = 0.05$ say), that the error $|d| \leq 0.5\sigma$ (or, equivalently, $|d/\sigma| \leq 0.5$). The above formula is then

$$\begin{aligned} n &= \left(z_{1-\alpha/2}\frac{\sigma}{d}\right)^2 \\ &= (1.96/0.5)^2 \approx 16 \end{aligned}$$

Early developmental trials
Testing a single mean

When the mean is tested then the one-sided null and alternative hypotheses are as follows:

$$H_0 : \mu \leq \mu_0 \text{ or } H_0 : \mu \geq \mu_0$$

versus, respectively,

$$H_A : \mu > \mu_0 \text{ or } H_A : \mu < \mu_0$$

or the two-sided null and alternative

$$H_0 : \mu = \mu_0$$

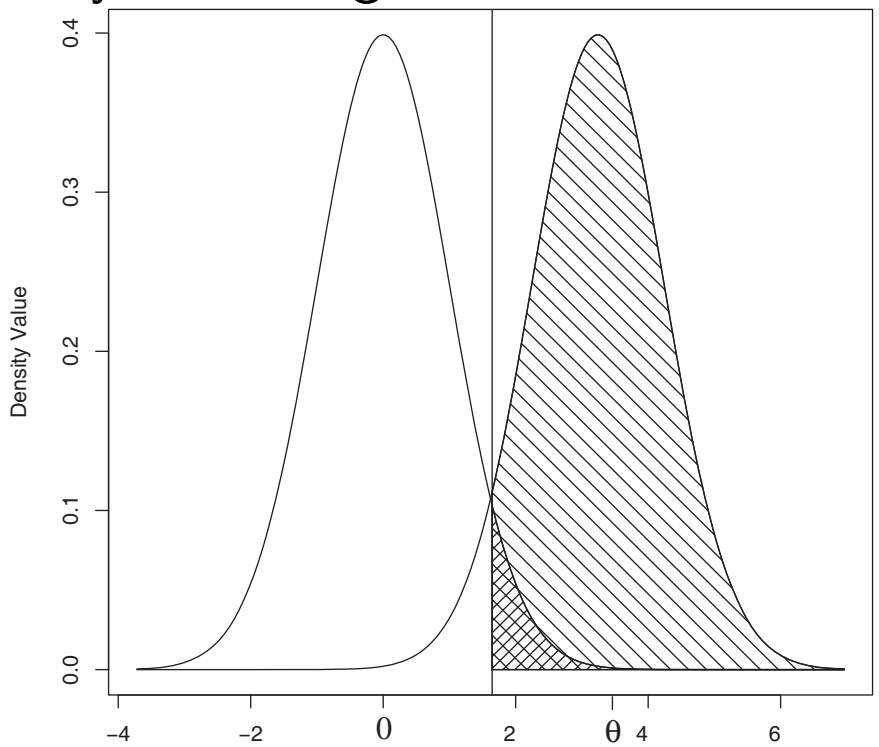
versus

$$H_A : \mu \neq \mu_0$$

Early developmental trials
Testing a single mean(continued)

Testing the null against the one-sided alternative $H_A : \mu = \mu_1 > \mu_0$, for a pre-specified value of μ_1 the test is based on the sample distribution of the mean $\bar{X}_n$ which, under H_0 is $N(\mu_0, \sigma^2/n)$ and under H_A $N(\mu_1, \sigma^2/n)$.

This is shown pictorially in the Figure below:



Early developmental trials
Sample size for testing a single mean

The distributions cutoff threshold x is given above so that $\Pr(\bar{X}_n \geq x) < \alpha$ and, simultaneously, $\Pr(\bar{X}_n \leq x) < \beta$, which is equivalent to $z_{1-\alpha} \geq \frac{x-\mu_0}{\sigma/\sqrt{n}}$ and $z_\beta \leq \frac{x-\mu_1}{\sigma/\sqrt{n}}$. Solving for x and equating the results we get

$$\mu_0 + z_{1-\alpha}\frac{\sigma}{\sqrt{n}} = \mu_1 + z_\beta \frac{\sigma}{\sqrt{n}}$$

Finally, solving for n we get

$$n = \frac{\sigma^2(z_{1-\alpha} - z_\beta)^2}{(\mu_1 - \mu_0)^2}$$

Note that we can express the equation above in terms of effect size $f = (\mu_1 - \mu_0)/\sigma$, i.e., $n = (z_{1-\alpha} - z_\beta)^2/f^2$.

Early developmental trials
Sample size for testing a single mean (continued)

As an example, consider the sample size required for a test of the hypothesis $H_0 : \mu \leq 3$ versus the alternative $H_A : \mu > \mu_0 = 4$ (this is completely contrived example). If the α and β levels are, respectively, 5% and 10% (or the power is 90%) and the standard deviation $\sigma = 2$, the required sample size will be

$$n = \frac{2^2[1.645 - (-1.282)]^2}{(4-3)^2} = 34.27$$

We choose the next integer as the sample size, so that $n \approx 35$. The same results would be generated by considering this difference in treatment means as an effect size $f = 0.5$.

Finally, in the case of a two-sided alternative hypothesis, the sample size would be $n = \frac{2^2[1.96-(-1.282)]^2}{(4-3)^2} \approx 43$.

Early developmental trials
Sample size for testing a single proportion

The above results can be modified by substituting $\sigma = \sqrt{p(1-p)}$ in the previous formula when testing for a single proportion (of toxicity or efficacy) p. In this case, the null hypothesis is $H_0 : p \leq p_o$ versus the one-sided alternative $H_A : p = p_1 > p_o$. The required sample size is

$$n = \frac{p_o(1-p_o)(z_{1-\alpha} - z_\beta)^2}{(p_1 - p_o)^2}$$

Thus, testing the null and alternative hypotheses $H_0 : p \leq 0.3$ and $H_A : p = 0.4$ respectively at the $\alpha = 0.05$ and $\beta = 0.10$ we have

$$n = \frac{0.3(1-0.3)(1.645 - (-1.282))^2}{(0.4-0.3)^2} \approx 180$$

Testing a single proportion
Single-stage design

Consider the following situation:

In a Phase II non-comparative study (i.e, a small study of one treatment that takes a first "stab" at efficacy assessment), we would like to know whether the true response rate is *at least* as high as 15% (the current standard).

Above that rate, the new therapy would be interesting and worth pursuing further, while, below this rate, we would discontinue development of the experimental therapy.

To perform power and sample size calculations we will have to specify an alternative rate $p_1 > p_0$. We set for this example, $p_1 = 0.40$.

Testing a single proportion
Statistical construction

The null hypothesis to be tested is

$$H_0 : p \leq p_0 = 0.15$$

versus the alternative

$$H_A : p > p_1 = 0.40$$

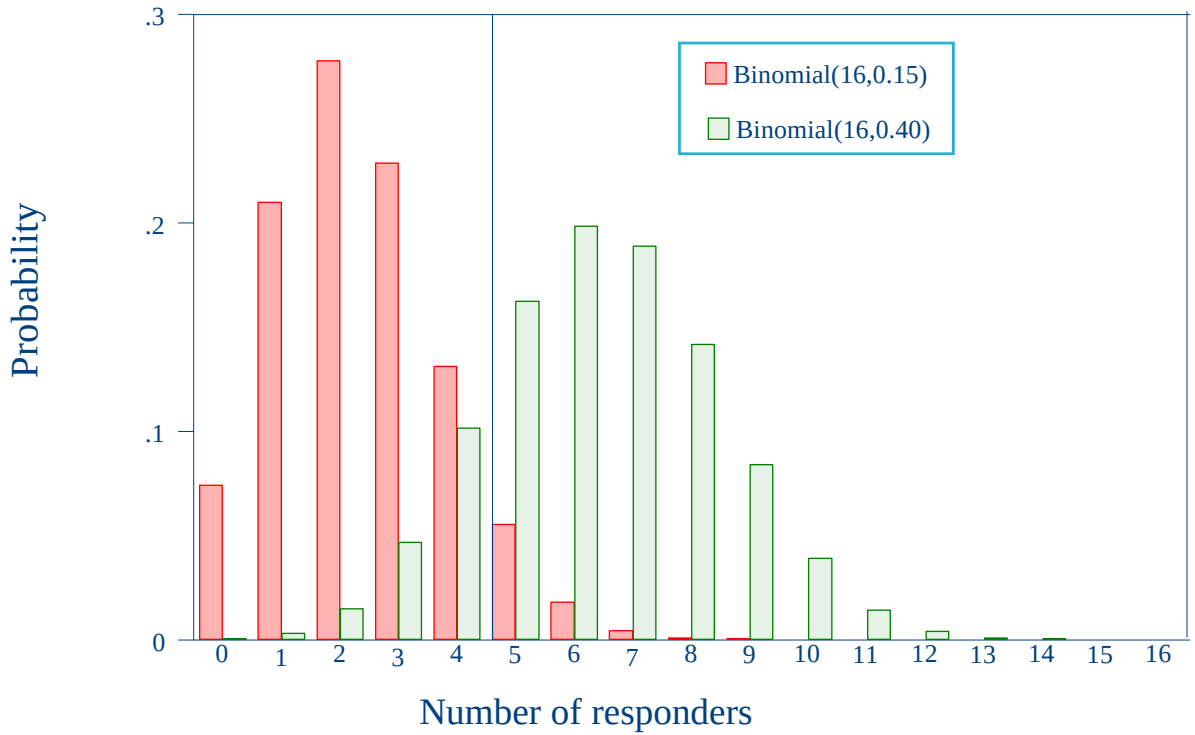
Let's say that we would like to maintain $\alpha \leq 0.1$ and the power $1 - \beta \approx 0.80$. We will thus create a one-sided 90% confidence interval with a lower bound and see whether this lower bound excludes (lies above) $p_0 = 0.15$.

The power is the chance that the confidence interval will lie above p_0 if the true response is p_1.

Monitoring toxicity is done in an identical manner by reversing the roles of p_0 and p_1 and H_0 and H_A above.

Testing a single proportion
Graphical representation of the problem

The situation is given graphically by the following figure:



Of course, unlike the continuous case, the above figure would not have been possible if we had not already determined the size n (see below for how this was done).

Testing a single proportion
Exact binomial confidence intervals

To determine the power at a specific sample size (or vice versa) we use the exact binomial distribution (e.g., Korn, *Biometrics*, 1986).

We work similarly to the one-sample continuous-data case by trying to identify a cutoff point x such that $\Pr(X \leq r|H_0) > 1 - \alpha$ and $\Pr(X \leq r|H_A) > 1 - \beta$. That is,

$$\sum_{k=0}^{r} \left(\begin{array}{c} n \\ k \end{array} \right) p_o^k (1 - p_o)^{n-k} > 1 - \alpha$$

and

$$\sum_{k=0}^{r} \left(\begin{array}{c} n \\ k \end{array} \right) p_1^k (1 - p_1)^{n-k} > 1 - \beta$$

Testing a single proportion
Statistical example

After some experimentation we end up with $n = 16$. In that case, the null hypothesis will be excluded if the number of responding patients is $X \geq 5$.

The alpha level of the test is the chance that $X \geq 5$ under the null hypothesis,

$$P(X \geq 5|H_0) = P(X \geq 5|n = 16, p = 0.15) = 0.0731 = \alpha$$

The power (or the chance that the CI will lie above p_0) is the same probability under the alternative hypothesis i.e.,

$$P(X \geq 5|H_A) = P(X \geq 5|n = 16, p = 0.40) = 0.8334 = 1 - \beta$$

Testing a single proportion
Statistical example

The null and alternative distributions $B(16, 0.15)$ and $B(16, 0.40)$:

k	$P(X = r\|H_0)$	$P(X \leq r\|H_0)$	$P(X = r\|H_A)$	$P(X \leq r\|H_A)$
0	.0743	.0742511	.0002821	.0002821
1	.2097	.2839012	.0030092	.0032913
2	.2775	.5613793	.0150459	.0183372
3	.2285	.7898907	.0468095	.0651467
4	.1311	**.9209**	.1014206	**.1666**
5	.0555	.9764556	.162273	.3288404
6	.0180	.9944137	.1983337	.5271741
7	.0045	.998941	.1888892	.7160634
8	.0009	.9998398	.1416669	.8577303
9	.0001	.9999807	.0839508	.941681
10	.0000	.9999982	.039177	.9808581
11	.0000	.9999999	.0142462	.9951043
12	.0000	1	.0039573	.9990615
13	.0000	1	.0008117	.9998733
14	.0000	1	.000116	.9999893
15	.0000	1	.0000103	.9999996
16	.0000	1	.0000000	1

Thus, the alpha level is $\alpha = 1 - 0.9209 = 0.0791$ and the power is $1 - \beta = 0.8334$.

Single-stage designs
The twostg program

We can obtain the quantiles of the binomial distribution by using the program twostg. For example, the first two columns in the table above can be generated as follows:

```
ENTER P AND N1: 0.15 16
   0      0.07425      0.07425
   1      0.20965      0.28390
   2      0.27748      0.56138
   3      0.22851      0.78989
   4      0.13106      0.92095
   5      0.05551      0.97646
   6      0.01796      0.99441
   7      0.00453      0.99894
   8      0.00090      0.99984
   9      0.00014      0.99998
  10      0.00002      1.00000
  11      0.00000      1.00000
  12      0.00000      1.00000
  13      0.00000      1.00000
  14      0.00000      1.00000
  15      0.00000      1.00000
  16      0.00000      1.00000
```

Single-stage designs
The rsppow and the toxpow programs

Two programs, developed at Harvard University and the Eastern Cooperative Oncology Group (ECOG) are the rsppow and the toxpow. They produce power calculations for studies estimating response and toxicity rates respectively.

The rsppow program helps with sample size calculation when the null hypothesis is that the response rate p is $H_0 : p \leq p_0$, versus the one-sided alternative $H_A : p = p_1 > p_0$.

The toxpow program helps with sample size calculation when the null hypothesis is that the toxicity rate p is $H_0 : p \geq p_0$ versus the one-sided alternative $H_A : p = p_1 < p_0$.

Single-stage designs
The rsppow and toxpow programs (continued)

In the example above, the input and output of the rsppow program looks as follows:

```
N, ALPHA, P1, P0 (P1>P0) (0 0 0 0 TO STOP): 16 0.1 0.4 .15
P0 EXCLUDED IF X.ge.  5
COVERAGE=0.9209
POWER   =0.8334
```

Single-stage designs

Suppose now that we wanted to mount a trial that would ensure, with at least 80% power and alpha level of 10% that the toxicity rate of a treatment were $p < 0.3 = p_0$ versus the expectation that the toxicity is truly $p_1 = 0.1$. Using toxpow we proceed as follows:

```
N, ALPHA, P1, P0 (P1<P0) (0 0 0 0 TO STOP): 21 .1 .1 .3
P0 EXCLUDED IF X.le.  3
COVERAGE=0.9144
POWER   =0.8480
```

Meaning that the exact attained alpha level is $\alpha = 1 - 0.9144 = 0.0856$ and power is $1 - \beta = 0.8480$.

Single-stage designs
The clinfun R package

There is an R package that performs much of these calculations. It is called clinfun and performs many clinical trial design calculations. The general invocation of function ph2single in this package is

```
ph2single(p0, p1, a, b, nsoln)
```

where `nsoln` provides a number of designs which would satisfy the α level and power requirement (although, usually the one with the smallest sample size is chosen).

Single-stage designs
The clinfun R package

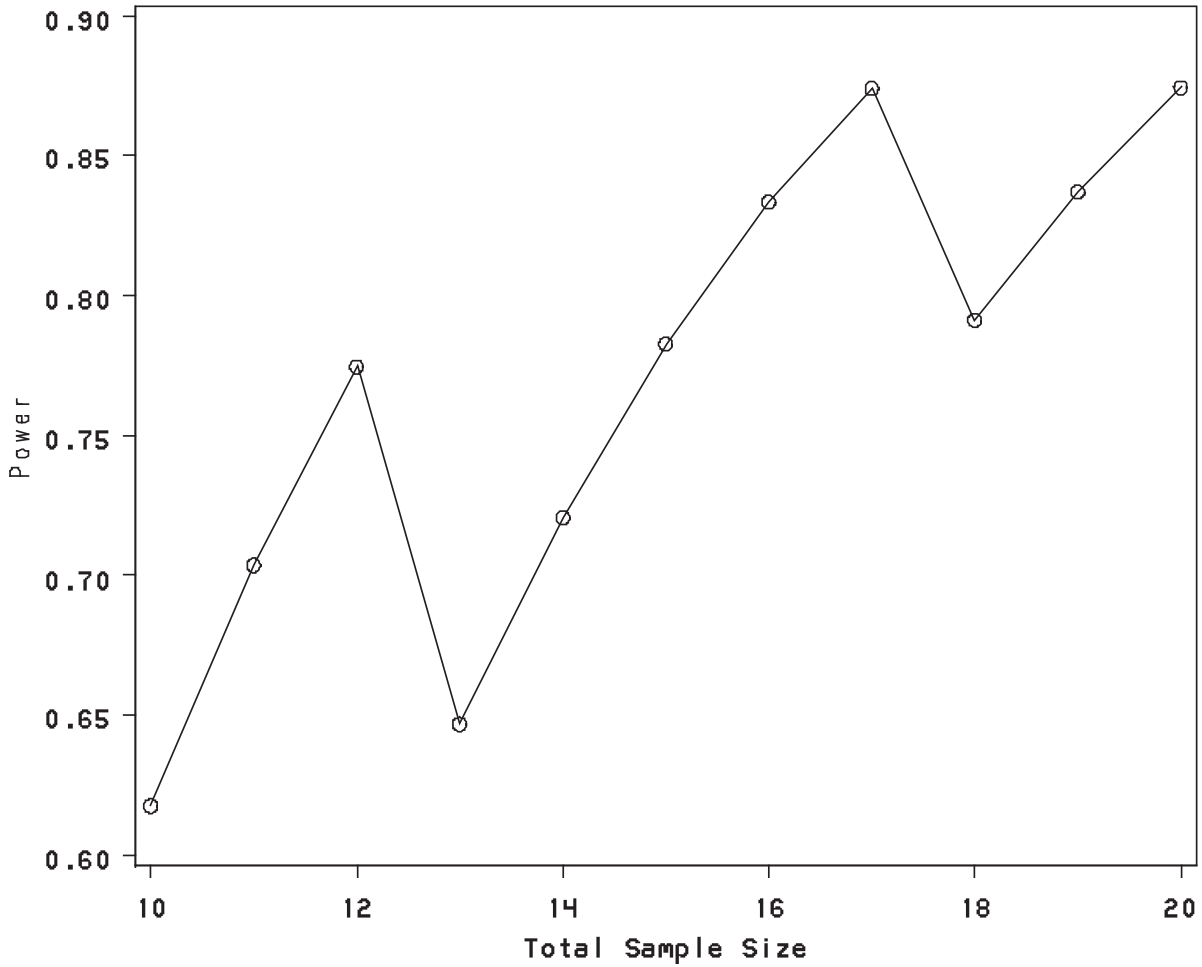
In our example, this is as follows:

```
> ph2single(.15, .4, .1, .2, nsoln=5)
   n r Type I error Type II error
1 16 4   0.07905130    0.16656738
2 17 4   0.09871000    0.12599913
3 19 5   0.05369611    0.16292248
4 20 5   0.06730797    0.12559897
5 21 5   0.08273475    0.09574016
```

for 5 designs. The first one is the design produced by the other software we considered earlier.

Testing a single proportion
Graphical output

The power above is shown graphically in the following figure.



Testing a single proportion
Two-stage designs

Consider what would be required in order to be able to insert an interim analysis (a first "stage") in the study monitoring. The components of a two-stage design are the following:

- Hypotheses to be tested
  - $H_0 : p \leq p_0$
  - $H_A : p \geq p_A$
- Type I (α), type II (β) errors and power ($1 - \beta$)
- Sample size (n) and total number of responses (r)
  - Stage I: Sample size (n_1) and number of responses (r_1)
  - Stage II: Sample size (n_2) and number of responses (r_2)

Two-stage designs attempt to control the alpha level and power.

Testing a single proportion
Simon's two-stage design

Simon (*Cont Clin Trials*, 1985) proposed the following design:

- **First stage**
  The study is stopped after the first stage for insufficient efficacy if r_1 or less responses out of n_1 total subjects are observed. The probability of early termination under rate p is

$$PET(p) = P(X \leq r_1 | n, p)$$

- **Second stage**
  The study is continued to the second stage if more than r_1 out of n_1 subjects respond during the first stage.
- The study is considered successful (H_0 is rejected) if more than $r = r_1 + r_2$ out of N subjects respond by the end of the second stage.

Simon's two-stage design
Expected versus maximum sample size

In the two-stage design the maximum sample size is random. The *expected* sample size (also known as *average sample number* or ASN) under rate p is given by the following formula:

$$\begin{aligned} ASN(p) &= n_1 + n_2 \times P(k > r_1 | n_1, p) \\ &= n_1 + n_2 \times (1 - PET(p)) \end{aligned}$$

that is, the average sample size equals the number of subjects to be enrolled in the first stage, times the number of subjects enrolled in the second stage probability of continuing to the second stage.

Simon's design minimizes $ASN(p_o)$ (i.e., under the null hypothesis)

The *minimax* design minimizes the maximum sample size n.

Simon's two-stage design
Implementation of the previous example

For example, consider the two-stage design with $n_1 = 9$, $r_1 = 1$, $n = 16$ and $r = 4$. Then under the null hypothesis $p = 0.15$ we have

n	$P(X = k \mid n = 9, p = 0.15)$	$P(X \leq k \mid n = 9, p = 0.15)$
0	0.23162	0.23162
1	0.36786	0.59948
2	0.25967	0.85915
3	0.10692	0.96607
4	0.02830	0.99437
5	0.00499	0.99937
6	0.00059	0.99995
7	0.00004	1.00000
8	0.00000	1.00000
9	0.00000	1.00000

With $r_1 = 1$ and $n_2 = 7$, $r_2 = 3$ (so that $r = 4$) we have

Probability of response $p = 0.15$

Stage I ($n_1 = 9$) responses	Stage II ($n_2 = 7$) responses	Probability	Cum. prob.
0		0.2316	0.2316
1		0.3679	0.5995
2	0	0.0832	0.6827
	1	0.1028	0.7856
	2	0.0544	0.8400
3	0	0.0343	0.8743
	1	0.0423	0.9166
4	0	0.0091	0.9257

Simon's two-stage design
Attained size of the test

The probability of not rejecting the null hypothesis $H_0 : p \leq 0.15$ when this is true is $1 - \alpha = 0.9257)$. The cumulative probability 0.9257 above is the total probability associated with all scenarios of non-rejection of H_0. These are:

- **First stage**
  The number of responses is $k \leq r_1 = 1$, i.e., $k = 0$, or 1 (this would result in stopping the trial).
- **Second stage**
  In order to proceed to the second stage, $k > 1$. In order *not* to reject the null hypothesis, $k \leq r = 4$, i.e., $k = 2, 3, 4$. The probability is given by summing the binomial probabilities of the compatible scenarios.

Thus, the attained size of the test is $\alpha = 1 - 0.9257 = 0.0743$.

Simon's two-stage design (cont'd)

To estimate power we run the same routine with $p = p_A = 0.40$. The results are as follows:

n	$P(X = k \mid n = 9, p = 0.40)$	$P(X \leq k \mid n = 9, p = 0.40)$
0	0.01008	0.01008
1	0.06047	0.07054
2	0.16124	0.23179
3	0.25082	0.48261
4	0.25082	0.73343
5	0.16722	0.90065
6	0.07432	0.97497
7	0.02123	0.99620
8	0.00354	0.99974
9	0.00026	1.00000

Simon's two-stage design (cont'd)

With $r_1 = 1$ and $n_2 = 7$, $r_2 = 3$ (so that $r = 4$) we have

Probability of response $p = 0.40$

Stage I ($n_1 = 9$) responses	Stage II ($n_2 = 7$) respnses	Probability	Cum. prob.
0		0.0101	0.0101
1		0.0605	0.0705
2	0	0.0045	0.0751
	1	0.0211	0.0961
	2	0.0421	0.1383
3	0	0.0070	0.1453
	1	0.0328	0.1780
4	0	0.0070	0.1851

Simon's two-stage design
Power

The previous output is interpreted as follows:

The probability of not rejecting the null hypothesis $H_0 : p \leq p_o = 0.15$ when this is false (i.e., the Type II of this test) is $\beta = 0.1851$.

The cumulative probability 0.1851 is given in a manner similar to the calculation of α above by summing the binomial probabilities of the compatible scenarios, but with $p = p_A$ in this case.

The projected power of this study is $1 - \beta = 0.8149$.

Simon's two-stage design
Using the twostg program: Alpha level

We can use the twostg program to obtain the exact alpha level and power in the previous design. This is done as follows:

```
   PROBABILITY OF RESPONSE =  0.1500

 ENTER P AND N1: .15 9
    0      0.23162      0.23162
    1      0.36786      0.59948
    2      0.25967      0.85915
    3      0.10692      0.96607
    4      0.02830      0.99437
    5      0.00499      0.99937
    6      0.00059      0.99995
    7      0.00004      1.00000
    8      0.00000      1.00000
    9      0.00000      1.00000
```

Simon's two-stage design

Using the twostg program: Alpha level (continued)

```
ENTER 1 FOR NEW P,N1, 0 OTHERWISE: 0

ENTER R1, N2, AND R2: 1 7 3

  STAGE I (N1 =  9)            STAGE II (N2 =  7)
      RESPONSES      RESPONSES      PROBABILITY      CUM. PROB.
-------------------------------------------------------------
          0                           0.2316           0.2316
          1                           0.3679           0.5995

          2              0            0.0832           0.6827
                         1            0.1028           0.7856
                         2            0.0544           0.8400

          3              0            0.0343           0.8743
                         1            0.0423           0.9166

          4              0            0.0091           0.9257
```

Simon's two-stage design

Using the twostg program: Power
To obtain the power of the two-stage design we proceed as follows:

```
ENTER 1 FOR NEW R1,N2,R2, 2 FOR NEW P,N1, 0 OTHERWISE: 2

ENTER P AND N1: 0.4 9
   0      0.01008      0.01008
   1      0.06047      0.07054
   2      0.16124      0.23179
   3      0.25082      0.48261
   4      0.25082      0.73343
   5      0.16722      0.90065
   6      0.07432      0.97497
   7      0.02123      0.99620
   8      0.00354      0.99974
   9      0.00026      1.00000
```

Simon's two-stage design

Using the twostg program: Power (continued)

```
ENTER 1 FOR NEW P,N1, 0 OTHERWISE: 0

ENTER R1, N2, AND R2: 1 7 3

  PROBABILITY OF RESPONSE =  0.4000

  STAGE I (N1 =  9)            STAGE II (N2 =  7)
     RESPONSES     RESPONSES     PROBABILITY     CUM. PROB.
-------------------------------------------------------------
          0                        0.0101          0.0101
          1                        0.0605          0.0705

          2             0          0.0045          0.0751
                        1          0.0211          0.0961
                        2          0.0421          0.1383

          3             0          0.0070          0.1453
                        1          0.0328          0.1780

          4             0          0.0070          0.1851

ENTER 1 FOR NEW R1,N2,R2, 2 FOR NEW P,N1, 0 OTHERWISE: 0
```

Simon's two-stage design
Average sample size

From the output above we can calculate that

- **Under the null hypothesis**

$$\begin{aligned} ASN(p_o) &= n_1 + n_2 \times (1 - B(r_1; n_1, p_o)) \\ &= 9 + 7 \times (1 - 0.59948) = 11.803 \end{aligned}$$

- **Under the alternative hypothesis**

$$\begin{aligned} ASN(p_A) &= n_1 + n_2 \times (1 - B(r_1; n_1, p_A)) \\ &= 9 + 7 \times (1 - 0.07054) = 15.506 \end{aligned}$$

The fact that the expected sample size of the two-stage design (under the null hypothesis) is significantly lower than the sample size of the comparable one-stage design is a critical advantage of this design.

Simon's two-stage design
The R package clinfun

To carry out a Simon or minimax two-stage design, we use the function ph2simon within the R package clinfun. The invocation of this function is

ph2simon(p0, p1, a, b, nmax)

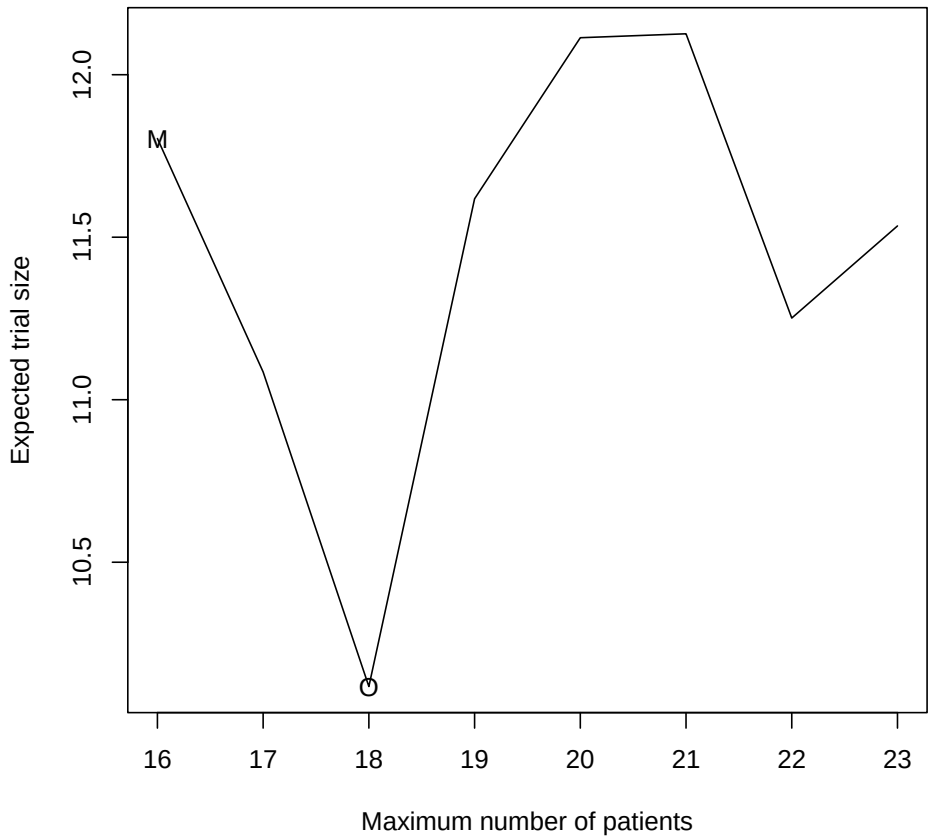
where nmax specifies the maximum n and is 100 by default unless you otherwise specify. In our previous example, the results are as follows:

```
 ph2simon(.15, .4, .1, .2)

 Simon 2-stage Phase II design

Unacceptable response rate:  0.15
Desirable response rate:  0.4
Error rates: alpha =  0.1 ; beta =  0.2

         r1 n1 r  n EN(p0) PET(p0)
Optimal   1  7 4 18  10.12  0.7166
Minimax   1  9 4 16  11.80  0.5995
```

Simon's two-stage design
Plotting the optimal (O) and minimax (M) designs

The previous output corresponding to optimal and the minimax designs is as follows:

```
plot(ph2simon(.15, .4, .1, .2))
```



Comparative studies
Testing the difference of two means

In the two-sample case, the null hypothesis is (usually) $H_0 : \mu_1 = \mu_2$. This is equivalent to difference of the two means $\hat{\Delta} = \bar{X}_1 - \bar{X}_2$ under some *a priori* assumptions.

The distribution of the sample difference of two means, assuming two equal-size $n_1 = n_2 = n$ (say) independent samples and known and equal variances ($\sigma_1^2 = \sigma_2^2 = \sigma^2$) is $\hat{\Delta} \sim N(\Delta, \sigma_\Delta^2)$, where $\sigma_\Delta^2 = \sigma^2 \left(\frac{1}{n_1} + \frac{1}{n_2}\right)$ and $\sigma_\Delta^2 = \left(\frac{2\sigma^2}{n}\right)$ if $n_1 = n_2 = n$.

In other words, the approach is the same as in the single-mean case, with the recognition that the variance is roughly double that of the one-sample case (to acknowledge the estimation of both μ_1 and μ_2.

Comparative studies
Sample size calculations

To calculate the sample size for each group n we can use the previous one-sample formula, with the appropriate estimate of the variance of course. That is, each group will be comprised of individuals from each population,

$$n\prime = \left[\frac{(z_\alpha + z_\beta)}{\Delta}\sigma_\Delta\right]^2 = \left[\frac{(z_\alpha + z_\beta)}{\Delta}\sigma\sqrt{2}\right]^2 = 2\left[\frac{(z_\alpha + z_\beta)}{\Delta}\sigma\right]^2 = 2n$$

where n is the size of the identically defined one-sample case. That is, the sample size in the two-sample case will be roughly double that of the one-sample case.

Comparative studies
Sample size calculations: effect size

We can also express the above formula in terms of the effect size $f = \Delta/\sigma$. In this case, the sample size will be

$$n\prime = \left[2\frac{(z_\alpha + z_\beta)}{f}\right]^2$$

For example, if $f = 0.25$, $\alpha = 0.05$ and $\beta = 0.1$ the required sample size will be

$$n\prime = \left[2\frac{(1.645 + 1.282)}{0.25}\right]^2 \approx 275$$

in each group for one-sided alternative hypotheses and

$$n\prime = \left[2\frac{(1.96 + 1.282)}{0.25}\right]^2 \approx 337$$

in each group for two-sided alternatives (see Piantadosi, 2005, pp.280).

Comparative studies
Testing for the difference in two proportions

In the two-sample case, the null hypothesis is (usually) $H_0 : \pi_1 = \pi_2$. This is equivalent to $H_0 : \delta = \pi_1 - \pi_2 = 0$.

Estimation of the difference of the true population proportions $\delta = \pi_1 - \pi_2$ is carried out by using the difference of the two sample proportions $\hat{\delta} = p_1 - p_2$ (where $p_1 = x_1/n_1$ and $p_2 = x_2/n_2$, i.e., the number of successes out of n_1 and n_2 failures in the two groups respectively).

Testing for the difference of two proportions (cont'd)

Under some suitable assumptions, the distribution of the difference of the two sample proportions is $\hat{\delta} \sim N(0, \sigma_\delta^2)$ under the null hypothesis and $N(\delta, \sigma_\delta^2)$ under the alternative hypothesis, where the variance is $\sigma_\delta^2 = \pi_1(1-\pi_1)\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$ under the null hypothesis (with $\sigma_\delta^2 = \frac{2\pi_1(1-\pi_1)}{n}$ when $n_1 = n_2 = n$), and $\sigma_\delta^2 = \frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}$ under the alternative (and $\sigma_\delta^2 = \frac{2\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}{n}$ when $n_1 = n_2 = n$).

Testing for the difference in two proportions Sample size calculations

With the exception of the fact that the variance is not the same under the null and alternative hypothesis (and, in fact, that the variance is a function of the unknown quantities π_1 and π_2), the approach is the same as in all previous illustrations.

To calculate the sample size for each group n (unequal sample sizes are handled fairly easily) we use a similar formula to the single-mean case, i.e.,

$$(\pi_1-\pi_0)+z_{1-\alpha}\sqrt{\frac{2\pi(1-\pi)}{n}} = (\pi_1-\pi_0)-z_{\beta}\sqrt{\sigma^2_{\delta} = \frac{2\pi_1(1-\pi_1)+\pi_2(1-\pi_2}{n}}$$

where, under the null hypothesis, $\pi_1 = \pi_2 = \pi$.

Testing for the difference in two proportions

The following is the formula for the sample size in the two-proportion case:

$$n = \frac{\left\{ z_{1-\alpha}\sqrt{2\pi(1-\pi)} - z_{\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)} \right\}^2}{(\pi_2-\pi_1)^2}$$

where, under the null hypothesis, $\pi_1 = \pi_2 = \pi$.

Testing for the difference in two proportions Example

For example, if $\pi_1 = 0.3$, $\pi_2 = 0.4$, $\alpha = 0.05$ and $\beta = 0.1$ (power=90%), $p = 1/2(0.3 + 0.4) = 0.35$ and the required sample size will be

$$n = \frac{\left\{1.645\sqrt{2(0.35)(0.65)} + 1.282\sqrt{(0.3)(0.7) + 0.4(0.6)}\right\}^2}{(0.4 - 0.3)^2} \approx 388$$

in each group for a one-sided alternative hypothesis and

$$n = \frac{\left\{1.96\sqrt{2(0.35)(0.65)} + 1.282\sqrt{(0.3)(0.7) + (0.4)(0.6)}\right\}^2}{(0.4 - 0.3)^2} \approx 477$$

in each group for two-sided alternatives.

Testing for the difference in two proportions Equality of means versus lack of association in a 2×2 table

The discussion here is a direct consequence of the 2×2 table setup, which is given below. Considering the "outcome" in the table as success (e.g., death, remission, toxicity, etc.) versus "failure") in the two groups, the table is set up as follows:

	Group		
Outcome	Group 1	Group 2	Total
Success	x_1	x_2	$x_1 + x_2$
Failure	$n - x_1$	$n - x_2$	$n - (x_1 + x_2)$
Total	n_1	n_2	$n = n_1 + n_2$

Then, the hypothesis of no difference between the two proportions (of "Success") is the same as the lack of *association* the outcome and membership in Group 1 or 2.

Testing for the difference in two proportions Using the Fisher's exact test

One way to address the case of lack of association is to use the, so-called, Fisher's exact test. According to this setup, the margins of the table above (i.e., the row and column totals) are considered fixed. Then the cell counts can be thought of as random draws of n_1 total colored balls from an urn, of which $x_1 + x_2$ have a certain color. x_1 has a *hypergeometric distribution*

$$P(X = x_1) = \frac{\begin{pmatrix} x_1 + x_2 \\ x_1 \end{pmatrix} \begin{pmatrix} n - (x_1 + x_2) \\ n - x_1 \end{pmatrix}}{\begin{pmatrix} n \\ n_1 \end{pmatrix}}$$

We can use the Fisher's exact test to calculate sample sizes in the previous example (this would be preferred, especially, in cases where the sample sizes are small and thus the normal approximation might not be appropriate).

Testing for the difference in two proportions Example using the Fisher's exact test in the R package clinfun

The R package clinfun has an array of different programs that use the 2×2 table setup. The function which corresponds to the Fisher's exact test is fe.ssize and is invoked as follows (shown are the default entries):

fe.ssize(p1, p2, alpha=0.05,power=0.8,r=1,npm=5,mmax=1000)

where r is the allocation ratio, npm is a range of $n \pm$npm where the sample calculation search will be conducted and mmax is the maximum group size.

Testing for the difference in two proportions Using the fe.ssize in the previous example

Using the function fe.ssize to calculate the sample size in the previous example we get

```
fe.ssize(.3, .4, alpha=0.1,power=0.9,r=1,npm=5,mmax=1000)
             Group 1 Group 2 Exact Power
CPS              408     408   0.9001173
Fisher Exact     408     408   0.9001173
```

for a one-sided alternative hypothesis (note that the routine will always give the two-sided alternative sample size so the alpha level must be doubled to get the one-sided sample size) and

```
fe.ssize(.3, .4, alpha=0.05,power=0.9,r=1,npm=5,mmax=1000)
             Group 1 Group 2 Exact Power
CPS              496     496   0.9003782
Fisher Exact     496     496   0.9003782
```

for a two-sided alternative. Along with the sample size corresponding to the Fisher's exact test, we also get the Casagrande, Pike and Smith approximation (*Biometrics*, 1978).

The concept of statistical information

The concept of statistical information is central to frequentist analysis. In general, the information about a parameter δ is

$$I \propto [\text{var}(\delta)]^{-1}$$

Thus, the information is proportional to the sample size in all of the cases so far described. For example, in the single-sample case $I \propto n/\sigma^2$, in the two-sample comparison $I \propto n/\sigma^2_\Delta$ and in the single-proportion case $I \propto \frac{n}{p(1-p)}$.

However, the statistical information in time-to-event trials that are based on the log-rank test is $I \propto D$, i.e., it is not proportional to the number of subjects but the number of events!

Statistical information
Studies of time to event

In the case of time to event studies, there are a number of considerations with respect to study design. These are:

- *Accrual of patients*.
  Accrual of patients happens at a rate of $a(t)$ over time.
- *Follow-up of patients*.
  Follow-up of patients happens over time $t - u$ after they have been accrued at time u.
- *Hazard* $\lambda(t)$.
  Hazard time $\lambda(t) = lim_{h \to 0} \frac{1}{h} \Pr(t \geq T \leq T + h | T \geq t)$, is the instantaneous tendency of failure.
- *Survival distribution* $S(t)$
  Survival distribution function is $S(t) = P(T \geq t)$ is the probability of survival past time t.

Time-to-event studies
Event rate

In order to have an event, each individual participating in the study must

- Have been accrued at time $u < t$
- Survived during the period $t - u$
- Had an event at time t

The event rate at time $t \leq T$ is given in general by the expression

$$n(t) = \int_0^\tau \underbrace{a(u)}_{\text{accrued at } u} \underbrace{S(t-u)}_{\text{survive past } t-u} \underbrace{\lambda(t-u)\,du}_{\text{fail at } t-u+h}$$

where $\tau = \min(t, T)$, so that

$$n(t) = \begin{cases} \int_0^t a(u)S(t-u)\lambda(t-u)du & \text{if } t \leq T \\ \int_0^T a(u)S(t-u)\lambda(t-u)du & \text{if } t > T \end{cases}$$

Time-to-event studies
Simplifying assumptions

Accrual is usually assumed to be uniform over the period $[0, T]$, i.e.,

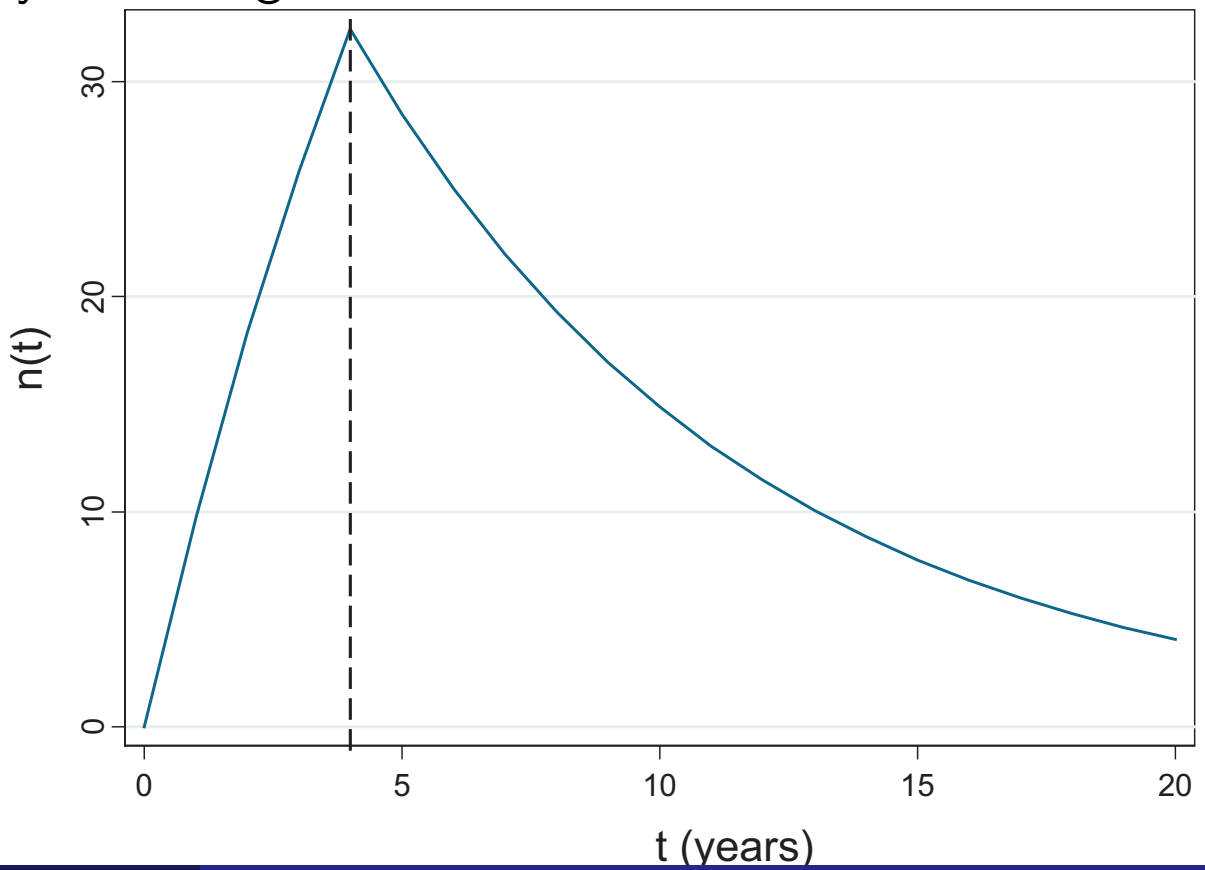
$$a(t) = \begin{cases} a_0 & \text{if } t \leq T, \\ 0 & \text{if } t > T \end{cases}$$

If the additional assumption is made that survival is exponential is made (i.e., $S(t) = \int_t^\infty \lambda e^{-\lambda u} du = e^{-\lambda t}$ and $\lambda(t) = \lambda$), the event rate at time t is

$$n(t) = \begin{cases} a_0 \int_0^t \lambda e^{-\lambda(t-u)} du = a_0(1 - e^{-\lambda t}) & \text{if } t \leq T, \\ a_0 \int_0^T \lambda e^{-\lambda(t-u)} du = a_0(e^{-\lambda(t-T)} - e^{-\lambda t}) & \text{if } t > T. \end{cases}$$

Time-to-event studies
Example (see Piantadosi, 2005, pp. 321-322)

Supposed that a clinical trial requires 180 events to achieve its planned power. If accrual proceeds at $a_0 = 80$ subjects annually, for $T = 4$ years, the event rate is constant at $\lambda = 0.13$ deaths per person-year of follow-up, the number of events is given graphically in the Figure below.



Time-to-event studies
Cumulative number of events

The number of total events is

$$D(t) = \int_0^t n(u)du$$

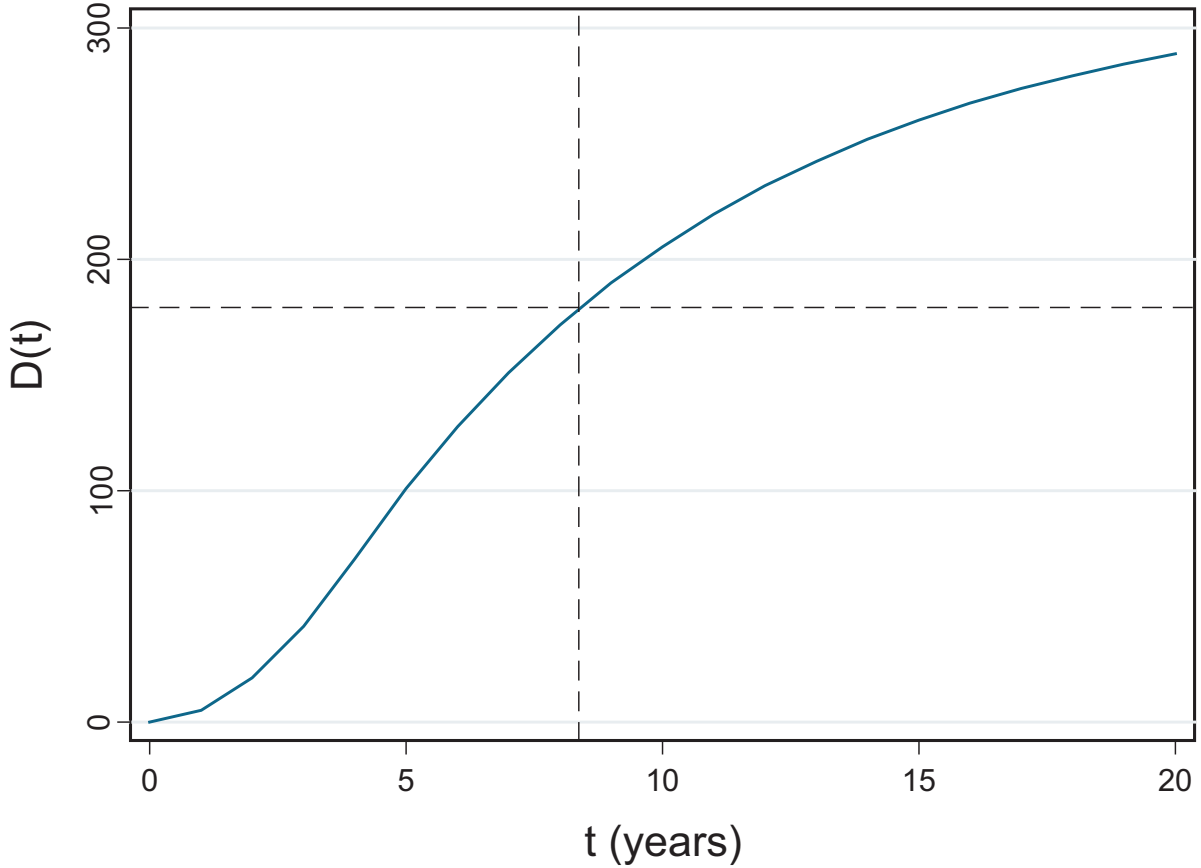
Using the previous simplifying assumptions of a uniform accrual and exponential survival, the cummulative number of events is

$$\begin{aligned} &\int_0^t a_0(1 - e^{-\lambda t})dt \\ &\qquad = \tfrac{a_0}{\lambda}(\lambda t + e^{-\lambda t} - 1) && \text{if } t \leq T \end{aligned}$$

$$\begin{aligned} &\int_0^T a_0(1 - e^{-\lambda t})dt + \int_T^t a_0(e^{-\lambda(t-T)} - e^{-\lambda t})dt \\ &\qquad = \tfrac{a_0}{\lambda}(\lambda T + e^{-\lambda t} - e^{-\lambda(t-T)}) && \text{if } t > T \end{aligned}$$

Clinical trial example
Cumulative number of events

In the previous example, the cumulative number of events is given graphically in the Figure below. Notice that it would take over five years after completion of accrual to reach the desired 180 number of events.



Designing survival studies
Number of events versus number of subjects

Designing studies with time to event as the endpoint, is challenging because we would like to, ultimately, determine the size of the sample. Given the complexities of the design, there is no single sample size that will fit the desired power considerations. So extensive experimentation is necessary. Here are some guidelines:

- If the cost of patient accrual is small relatively to the cost of a long study and accrual rates are fixed, we can accelerate the completion of the study by increasing the sample size (i.e., extending accrual versus extending follow-up). Alternatively, if we can, accrual rates can be increased by incorporating more sites.
- If the cost of patient accrual is great, we can accrue less patients (although never of course less than the desired number of events) and follow them longer (so that we can observe a larger proportion of them having the event)

Introduction to clinical trials

Unmatched case-control studies

The discussion here is a direct consequence of the 2×2 table setup described previously. Considering the "outcome" in that table as the exposure (i.e., "Exposed" versus "Not-exposed") the table is set up as follows:

	Group		
Exposure	Group 1	Group 2	Total
Exposed	x_1	x_2	$x_1 + x_2$
Not exposed	$n - x_1$	$n - x_2$	$n - (x_1 + x_2)$
Total	n_1	n_2	$n = n_1 + n_2$

Risk versus odds ratio

In the previous table, the ratio of the risk of exposure in Group 1 versus Group 2 R is estimated by $\hat{R} = \frac{x_1/n_1}{x_2/n_2}$. The ratio of the *odds* of exposure versus non-exposure in the two groups (the odds ratio) is given by

$$\hat{\psi} = \frac{\frac{x_1/n_1}{(n_1-x_1)/n_1}}{\frac{x_2/n_2}{(n_2-x_2)/n_2}} \approx \hat{R}$$

for a *rare* exposure levels since $\frac{(n_1-x_1)/n_1}{(n_2-x_2)/n_2} \approx 1$ allowing the use of the odds ratio, which has attractive mathematical properties rather than the risk ratio in inference (and thus in sample-size calculations).

Also recall that, in 2×2 tables the odds ratio is $\hat{\psi} = \frac{x_1(n-x_2)}{(n-x_1)x_2}$, with (see e.g., Schlesselman, 1982).

Sample size formula for unmatched case-control studies

Recall that the sample-size formula for comparing two proportion is

$$n = \left[z_{1-\alpha} \sqrt{2p(1-p)} - z_{\beta} \sqrt{p_0(1-p_0) + p_1(1-p_1)} \right]^2 / (p_1 - p_0)^2$$

(with $z_{1-\alpha/2}$ replacing $z_{1-\alpha}$ in the case of a two-sided alternative hypothesis) and $p = 1/2(p_0 + p_1)$.

We can use the same formula to estimate the sample size of an unmatched case-control study (recall our discussion about the equivalence of the Pearson chi-square test and the test of the difference in two proportions using the normal approximation) but instead of specifying the null and alternative proportions p_0 and p_1 we will input the null proportion p_0 and the odds ratio ψ.

Sample size formula for unmatched case-control studies (continued)

Then, we will derive

$$\begin{aligned} \pi_1 &= \frac{\pi_0 R}{[1+\pi_0(R-1)]} \\ &= \frac{\pi_0 \psi}{[1+\pi_0(\psi-1)]} \end{aligned}$$

and proceed as usual (in fact we will no longer use the risk ratio, assuming approximate equality with the odds ratio).

Example:Oral-contraceptives and benign breast disease*

We assume that 20% of women in the control group use oral contraceptives $\pi_0 = 0.2$ and we would like to be able to detect a reduction of risk for benign breast disease of 30% (i.e., $R \approx \psi = 0.7$) in the comparison group. This implies directly that the oral-contraceptive use in the comparison group (i.e., among cases) associated with a 30% reduction in risk will be

$$\pi_1 = \frac{0.2(0.7)}{[1 + 0.2(0.7 - 1)]} = 0.1489$$

Then, $p = 1/2(0.2 + 0.1489) = 0.1745$ and the required sample size will be

$$\begin{aligned} n &= \frac{\left[1.96\sqrt{2[0.1745(1-0.1745)]} + 1.282\sqrt{0.2(1-0.2) + 0.1489(1-0.1489)}\right]^2}{(0.1489 - 0.2)^2} \\ &\approx 1158 \end{aligned}$$

It would take 1,158 individuals *per group* to detect an odds ratio of $\psi = 0.7$, with null proportion $\pi_0 = 0.2$, 90% power and 5% alpha level.

*Schlesselman, 1982, pp.147).

Computer implementation

We can do this with SAS, using the approach we discussed before for comparing to proportions. The only difference is that the second proportion will not be determined directly but through the equation

$$p_2 = \frac{x_2}{n_2} = \frac{p_1\psi}{[1 + p_1(\psi - 1)]}$$

The code is as follows:

```
proc power;
   twosamplefreq test=pchi
      refproportion= .2
      oddsratio = .7
      npergroup = .
      power = 0.9;
run;
```

Output

The output from the SAS code above is

The POWER Procedure
Pearson Chi-square Test for Two Proportions

Fixed Scenario Elements

Distribution	Asymptotic normal
Method	Normal approximation
Reference (Group 1) Proportion	0.2
Odds Ratio	0.7
Nominal Power	0.9
Number of Sides	2
Null Odds Ratio	1
Alpha	0.05

Computed N Per Group

Actual Power	N Per Group
0.900	1159

So the results are identical to what we calculated by hand.

Multiple controls per case

An extension of the previous sample-size equations for the case of m controls for each case is as follows:

$$n = \frac{\left[z_{1-\alpha}\sqrt{(1+1/m)p(1-p)} - z_{\beta}\sqrt{p_0(1-p_0)/m + p_1(1-p_1)}\right]^2}{(p_1 - p_0)^2}$$

with

$$p = (mp_1 + p_2)/(1+c)$$

Example: Case control study of congenital heart disease

Thus, for example, in a case control study of congenital heart disease with $m = 2$ controls per case and assume that $\psi = 4$, $\alpha = 0.05$ (two-sided), power of 90% and null proportion $\pi_0 = 0.3$.

Then $p_2 = 0.3(4)/[1 + 0.3(4 - 1)] = 0.6316$ and
$p = [2(0.3) + 0.6316]/(1 + 2) = 0.4105$ and the sample size is

$$\begin{aligned} n &= \frac{\left[1.96\sqrt{(1 + 1/2)0.4105(1 - 0.4105)} + 1.282\sqrt{0.3(1 - 0.3)/2 + 0.6316(1 - 0.6316)}\right]^2}{(0.6316 - 0.3)^2} \\ &\approx 34 \end{aligned}$$

Thus, we require $n = 34$ cases and $mn = 2(34) = 68$ controls.

Implementation with SAS

To do this with SAS we use the following code:

```
proc power;
   twosamplefreq test=pchi
      refproportion= .3
      oddsratio = 4
      ntotal = .
      groupweights=(1 2)
      power = 0.9;
run;
```

Output

The output of the previous code is:

The POWER Procedure
Pearson Chi-square Test for Two Proportions
Fixed Scenario Elements

Distribution	Asymptotic normal
Method	Normal approximation
Reference (Group 1) Proportion	0.3
Odds Ratio	4
Group 1 Weight	1
Group 2 Weight	2
Nominal Power	0.9
Number of Sides	2
Null Odds Ratio	1
Alpha	0.05

Computed N	Total
Actual Power	N Total
0.901	102

Which means that a total of 102 subjects (34 cases and 68 controls) are needed.

Matched case control studies

Consider the following example (Pagano & Gauvreau, 2000, pp. 350) regarding the relationship between myocardial infarction (MI) and diabetes. In this example, 144 Navajo Indians that had experienced MI were matched by age and gender to 144 individuals free of heart disease. The results for the 144 matched pairs are given in the 2×2 table below:

	No MI		
MI	**Diabetes**	**No Diabetes**	**Total**
Diabetes	9	37	46
No Diabetes	16	82	98
Total	25	119	144

Setup

Out of the 46 Navajos with heart disease and diabetes, 9 were matched with individuals with diabetes and 37 were matched with individuals with no diabetes. Out of the 98 subjects with heart disease that did not have diabetes, 16 were matched with diabetics and 82 with non-diabetics.

The table in general is as follows:

	Control		
Case	**+**	**-**	**Total**
+	A	B	$A+B$
-	C	D	$C+D$
Total	$A+C$	$B+D$	N

Information and discordant pairs

In the previous table, all information about the difference in the proportion of exposed cases $(A + B)/N$ versus exposed controls, $(A + C)/N$, i.e., $(B - C)/N$ is provided by the *discordant* pairs B and C, i.e., the pairings of an exposed case with an unexposed control and vice versa.

In our example there are $B = 37$ pairs with the MI member being a diabetic and the non-MI member being a non-diabetic and $C = 16$ pairs where the MI member suffers from diabetes but the non-MI member does not.

Sample size calculations
Number of discordant pairs

The formula giving the sample size is derived through a number of steps. First, we need to estimate the number of discordant pairs which will be required. This is given by the following formula (e.g., Schlesselman, 1982):

$$m = \frac{\left[z_\alpha - z_\beta \sqrt{P(1-P)}\right]^2}{(P - 1/2)^2}$$

where $P = \psi/(1+\psi) \approx R/(1+R)$.

Sample size calculations
Number of subjects

To obtain the number of subjects required in the study, we consider the fact that, if p_e is the probability of an exposure-discordant pair (i.e., C/N), then the total number M required to yield m discordant pairs is

$$M = m/p_e$$

Now, the probability of an exposure-discordant pair is*

$$p_e \simeq p1(1-p_0) + (1-p_1)p_0$$

where, as before, $p_1 = p_0 R/[1 + p_0(R-1)]$.

So that

$$M \simeq m/(p_0(1-p_1) + p_1(1-p_0)$$

Example: Oral contraceptive and congenital heart disease

As an example, consider the matched case-control study of oral contraceptive and congenital heart disease. If the proportion of the exposed controls is $p_0 = 0.3$, $\alpha = 0.05$ (two-sided) and $\beta = 0.1$, in order to detect a two-fold increase in relative risk ($R = 2$), then $P \approx 2/3$ and we will need

$$m = \frac{\left[1.96/2 + 1.282\sqrt{(2/3)(1/3)}\right]^2}{(2/3 - 1/2)^2} = 91$$

$m = 91$ discordant pairs. Calculating $p_1 = 0.3(2)/[1 + 0.3(2-1)] = 0.46$, then,$p_e \simeq (0.3)(1 - 0.46) + 0.46(1 - 0.3) = 0.484$ and, finally,

$$M \simeq 91/0.484 = 188$$

Thus, the total sample size required would consist of $M = 188$ pairs (or 188 subjects per group).