Sample Size and Power III: Time to Event Outcomes

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Time to Event Endpoints

In many clinical trials, the primary endpoint is the time to an event, e.g., death or disease progression.

In that circumstance, the analyst will employ methods specific to the analysis of "survival data".

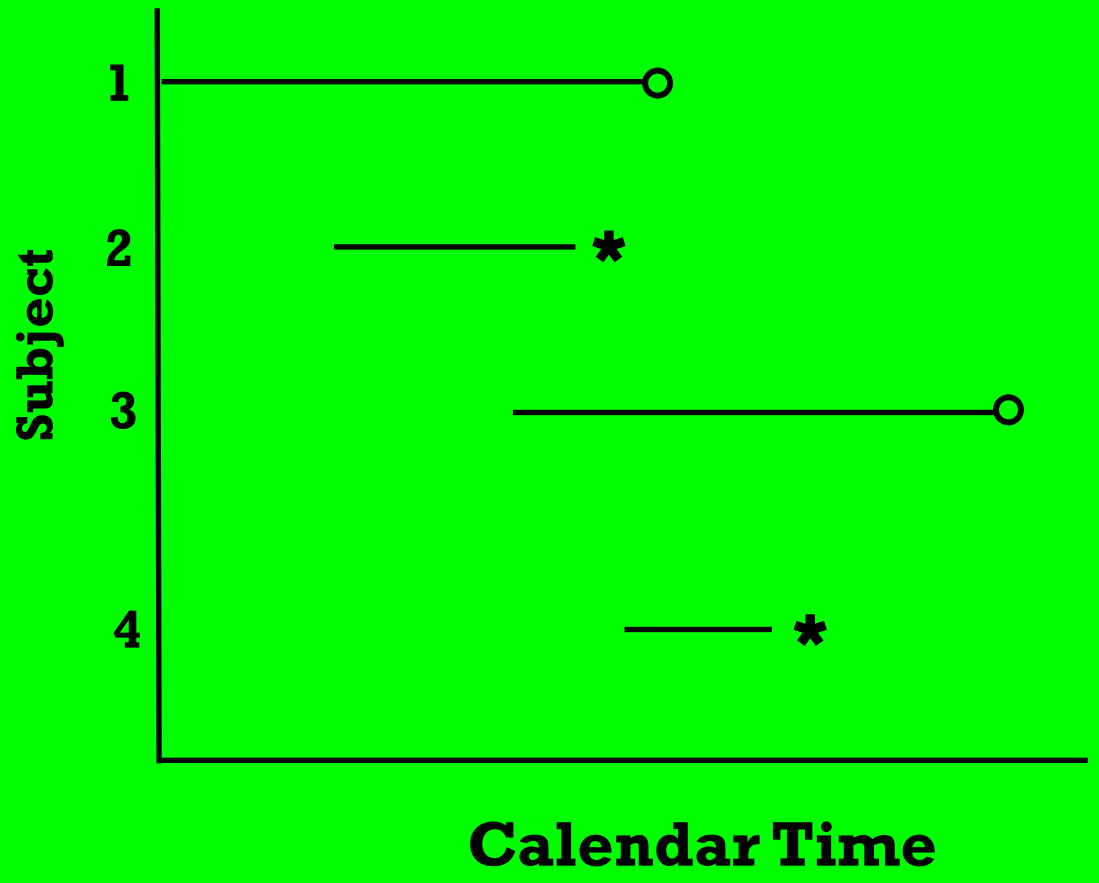
We discuss those methods briefly here, but in greater detail later in the course.

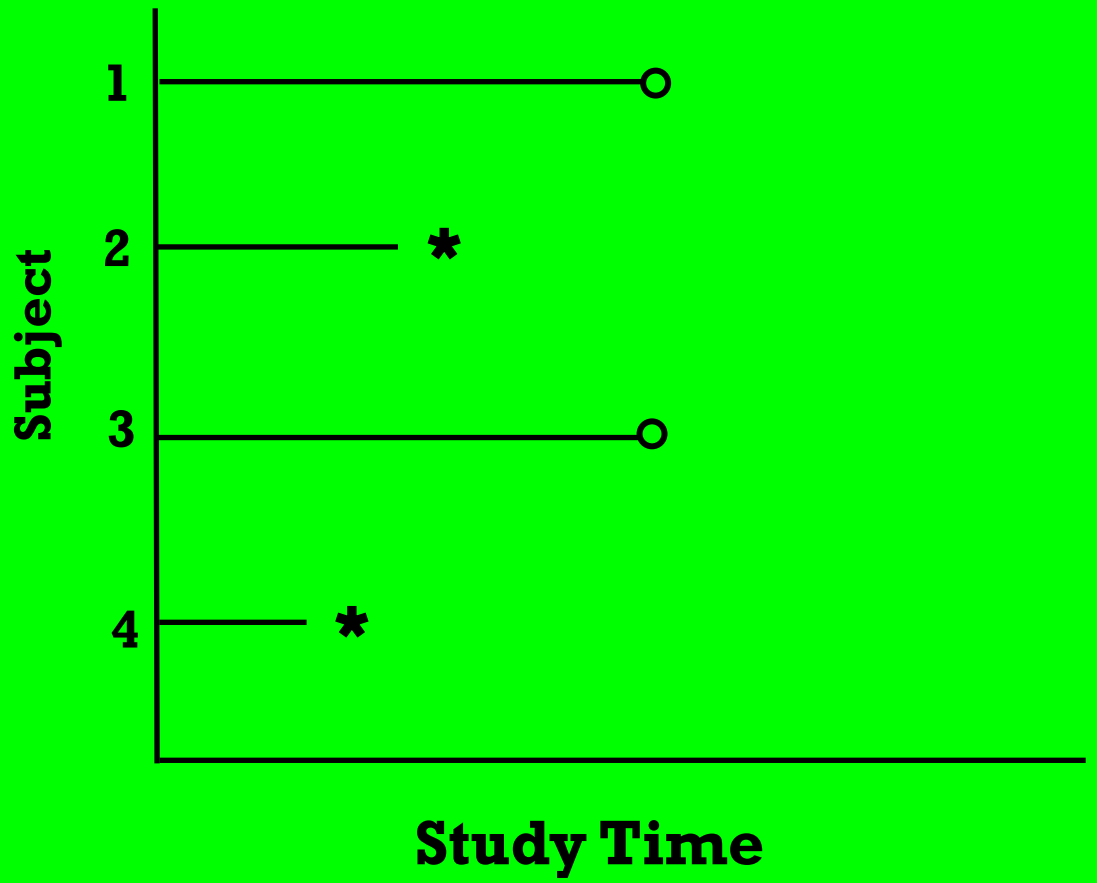
Analysis of Survival Data

Basic approach:

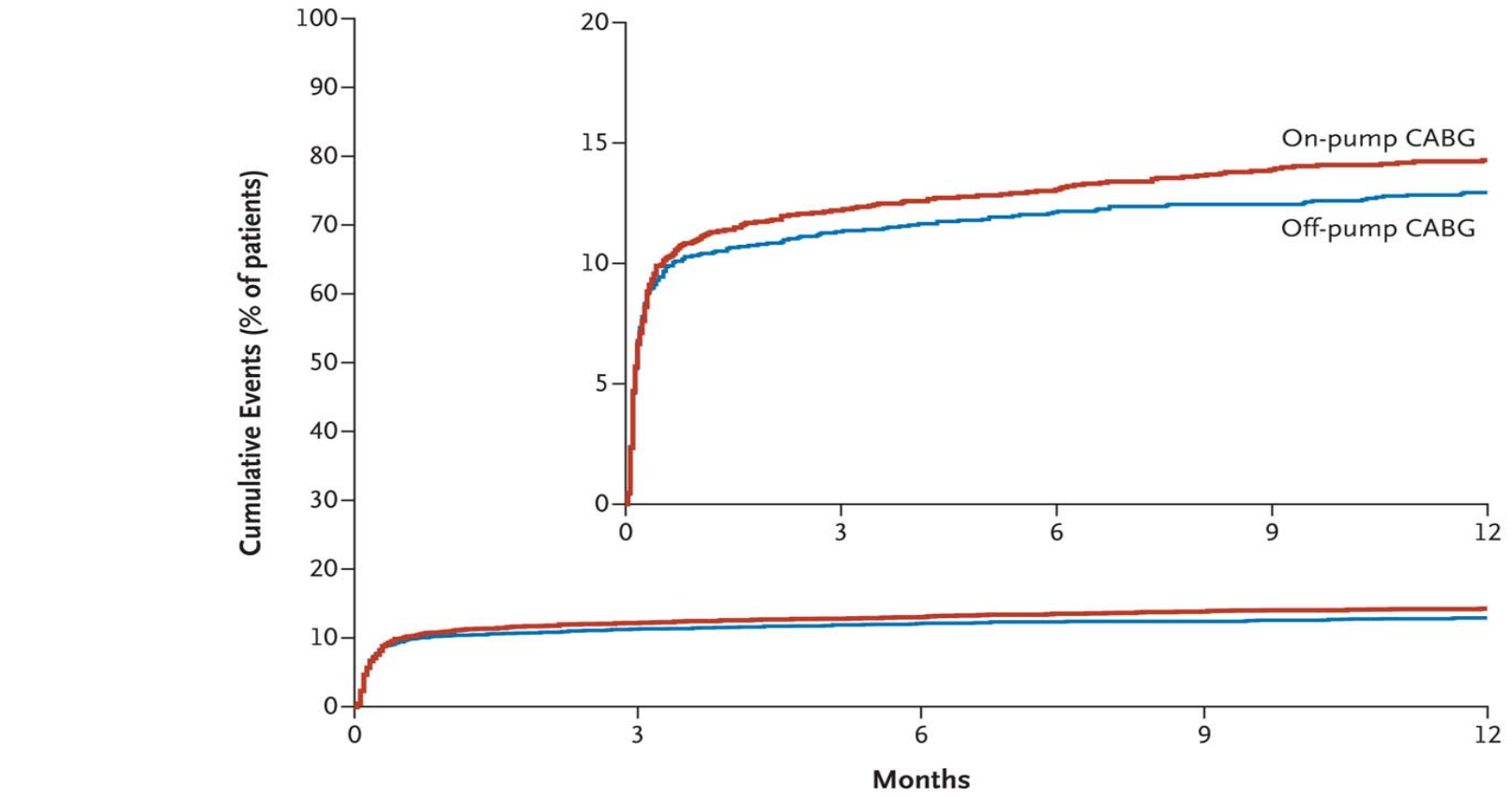
Estimate the survival distribution in each treatment group and use nonparametric methods to compare them. The most common test is known as the log-rank test.

Modern methods accommodate variable entry times and periods of follow-up


Subject
1
2
3
4
Calendar Time


1
2
3
4
Subject
Study Time

Kaplan–Meier Curves for the Primary Outcome in the CORONARY Trial.



No. at Risk					
Off-pump CABG	2375	2115	2097	2069	2054
On-pump CABG	2377	2098	2080	2044	2032

Lamy A et al. N Engl J Med 2013;368:1179-1188

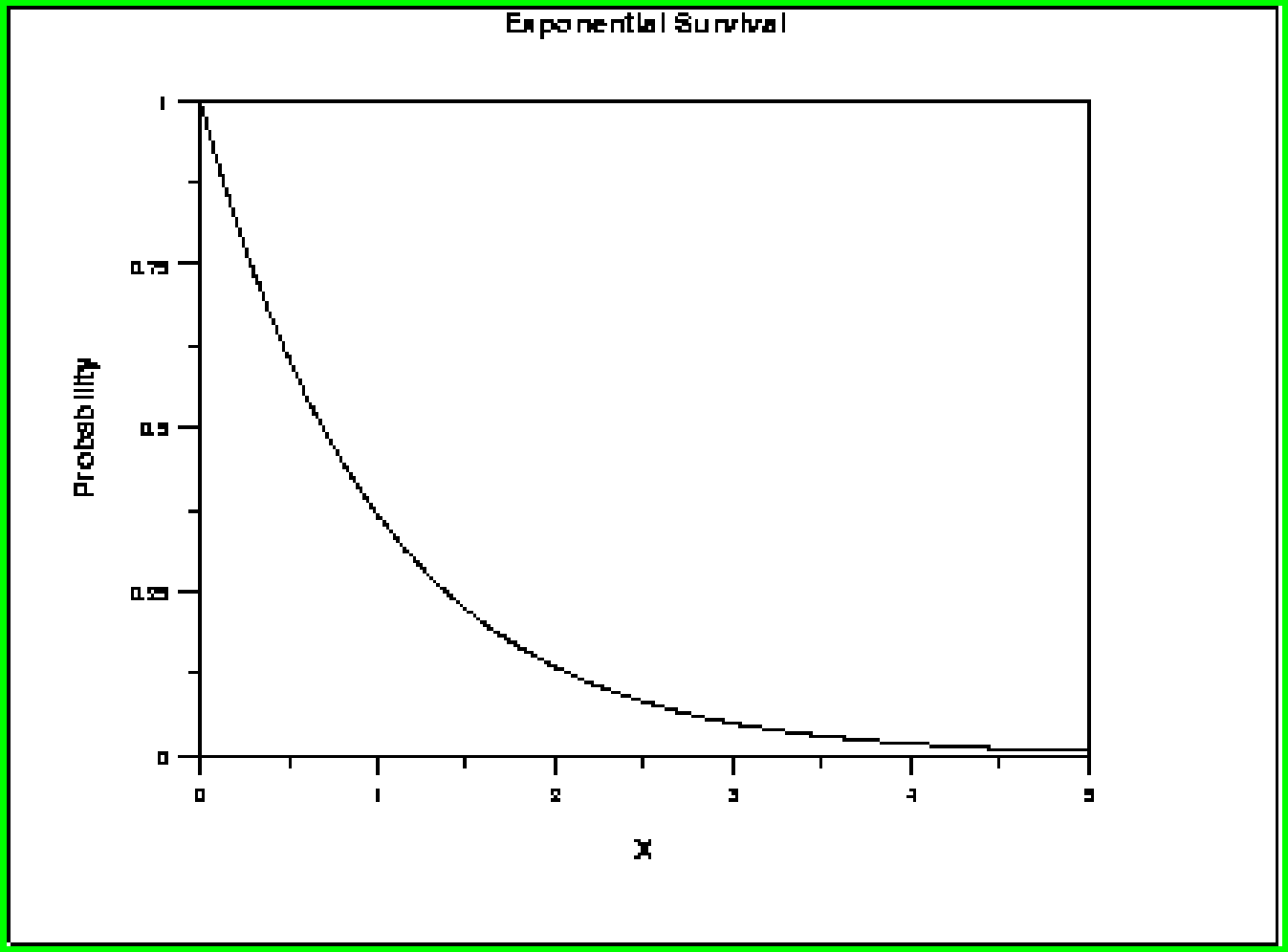
Time to Event Endpoints

For sample size calculations, we sometimes assume that the survival distribution, S(t), is exponential,

$$S(t) = P(\text{Patient Survives beyond } t) = \exp(-\lambda t)$$

where λ is the hazard rate or force of mortality

In the exponential model, the survival distributions are complete characterized by λ


Exponential Survival
Probability
1
0.75
0.5
0.25
0
0
1
2
3
4
5
X

Time to Event Endpoints

With exponential survival distributions, the null hypothesis is

$$H_0: \lambda_T = \lambda_C$$

A simple formula for the sample size, assuming all subjects are followed to the event, is

$$n = 2(Z_{\alpha/2} + Z_{\beta})^2/[\ln(\lambda_C/\lambda_T)]^2$$

where the values of λ_C and λ_T are given by H_a

Time to Event Outcomes

When subjects are recruited over a period of time and the study ends when some subjects have not had the event, sample size calculations are more complex

Lachin[1] gives a general formula

$$n = (Z_{\alpha/2} + Z_{\beta})^2[\varphi(\lambda_T) + \varphi(\lambda_C)]/(\lambda_T - \lambda_C)^2$$

Important Point. The sample size depends on the recruitment and follow-up schedules

The logrank Test

The standard nonparametric test for comparing two distributions is the logrank test.

Interestingly, sample size formulas for the logrank test are closely related to those that apply when the times-to-event follow an exponential distribution

Event-Driven Trials

For the logrank test, the power of the study depends on the number of events observed. This has led to the concept of the event-driven trial.

Schoenfeld[9] showed that, if the logrank test will be used to compare two time-to-event distributions, the number of events required to achieve power of 1 - β is

$$d = 4(Z_{\alpha/2} + Z_{\beta})^2/[\ln(\lambda_C/\lambda_T)]^2$$

What To Do if the Estimated Sample Size is not Feasible

1. Check your method and your calculations
2. Is the effect size unreasonably small or the assumed variance too large?
3. Is it reasonable to increase Type 1 or Type 2 error?
4. Choose continuous primary outcomes
5. Choose outcomes that have smaller variance
6. Consider surrogate variables

Choose binary outcomes that are more common

Be realistic! An underpowered study is a bad investment for everyone

What to Do if you Don't Have the Necessary Information

1. Search the literature carefully
2. Use approximate methods to estimate missing variables

   For approximately normal variables, the standard deviation is approximately ¼ of the range of common values
3. Conduct a pilot study
4. Dichotomize the variable
5. Make an educated guess

Sources for Sample Size Determination

Though most sample size calculations follow a pattern based on a normal approximation to the test statistic, details are always a bit complicated.

Sample size calculations often account for non-adherence and loss-to-follow-up

It's best to find a reliable source and obtain sample sizes by formula or table.

Software

PS – Free Software from Vanderbilt

http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize

STATA

EAST

PASS

Web Resources

UCLA http://calculators.stat.ucla.edu/powercalc/

- Normal, Exponential, Binomial, Poisson
- Sample Size and Power Calculations

MGH: http://hedwig.mgh.harvard.edu/sample_size/size.html

- Binomial (Parallel or Cross-over Trial)
- Normal (Parallel or Cross-over Trial)
- Time to Event

Statpages: http://statpages.org/

- An excellent compendium of online statistical tools

Literature Sources for Sample Size Formulas and Tables

Binary Outcomes	References 2 – 4
Measured Outcomes	
Nonparametric Test	Reference 5
Parametric Tests	References 6 – 9
Time to Event Outcomes	References 10-11

References

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