



Sample size: a couple more hints to handle it right using SAS and R

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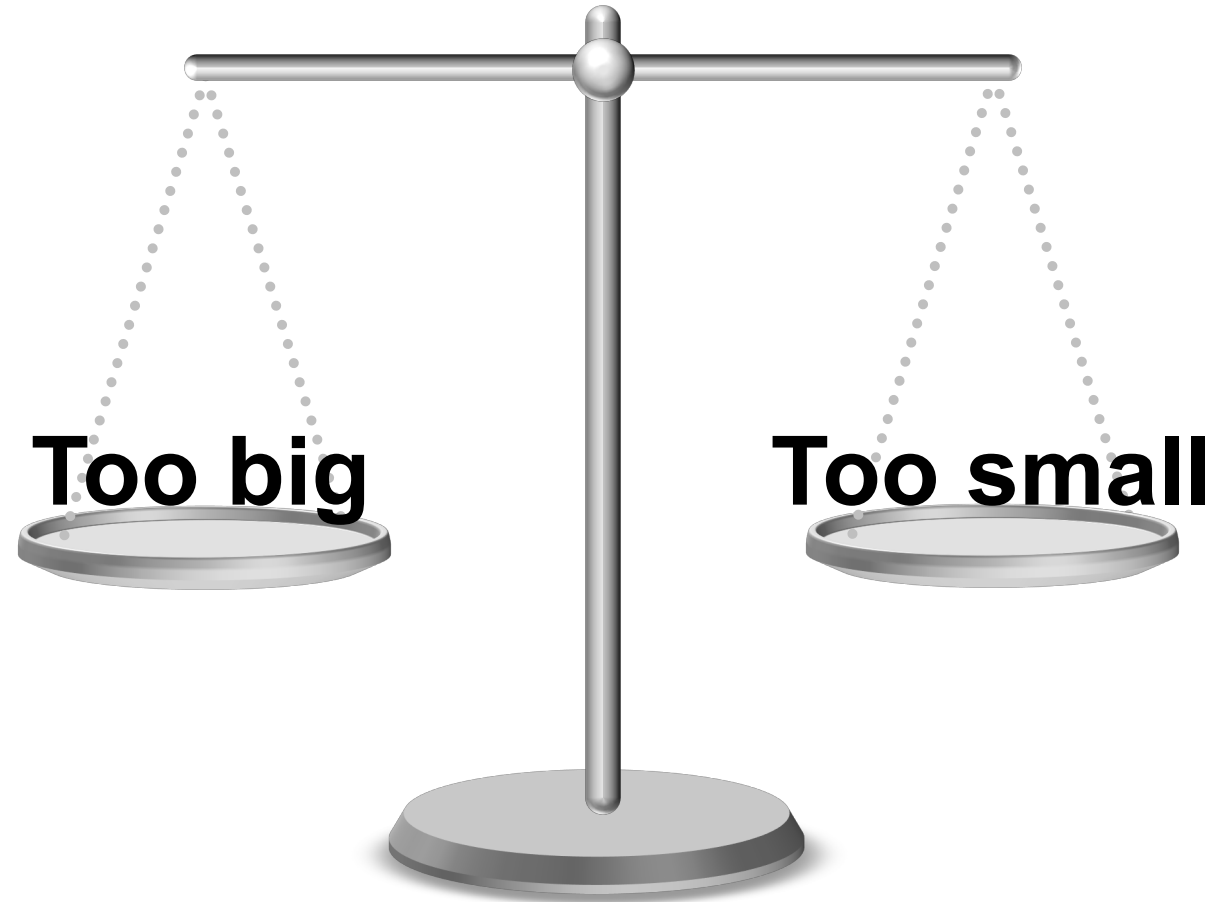


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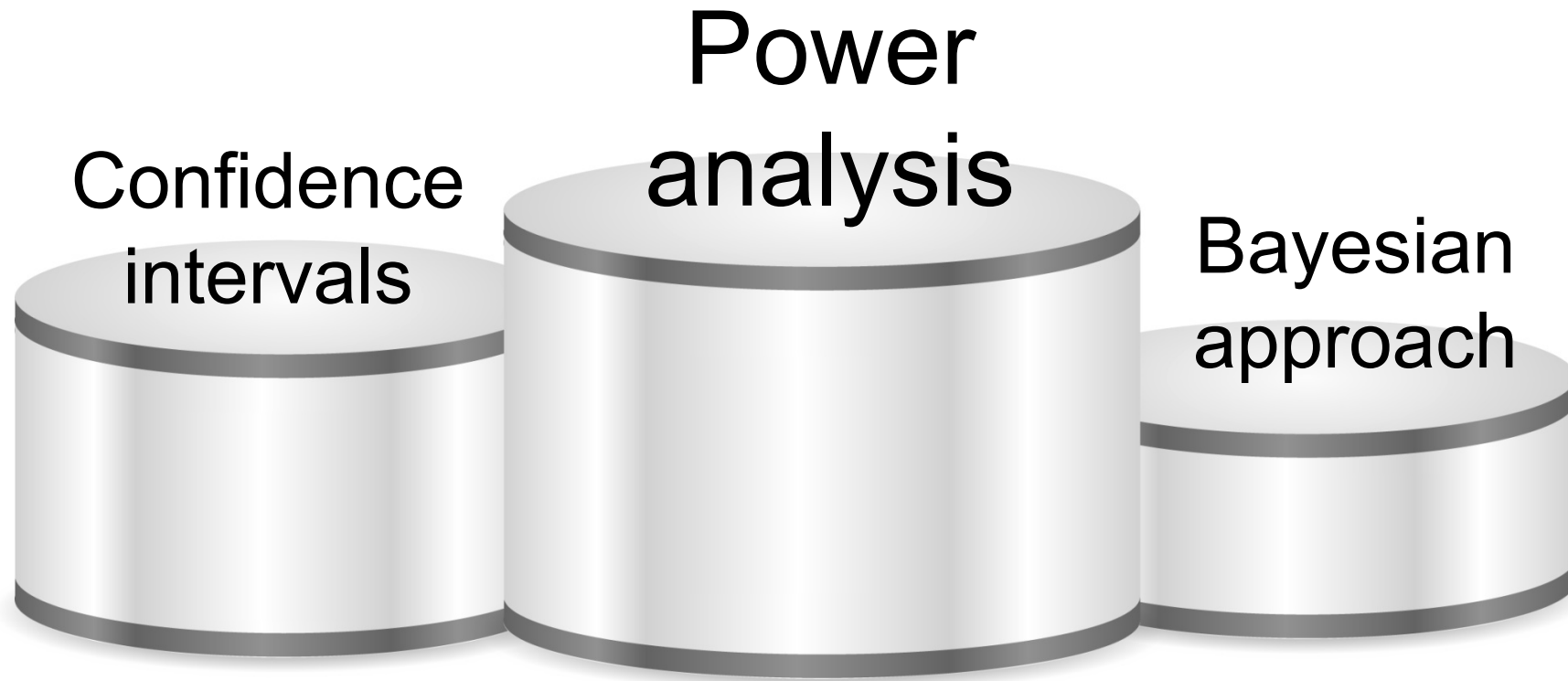
Why is it needed?

A clinical trial must be carefully planned to achieve its objectives. Estimation of the sample size is an important part of planning a clinical trial – and usually a difficult one

Balance is important



Methods of estimation



What affects the sample size

- Level of significance
- Power of the criterion
- Data variability
- Least expected treatment effect

What affects the sample size

- **Level of significance**

Sample size grows as the level of significance decreases, as well as decreases the probability of making type I error, i.e. probability of rejecting the tested hypothesis when it is correct. In practice, it is assumed to be 0.05 or 0.01

- Power of the criterion
- Data variability
- Least expected treatment effect

What affects the sample size

- Level of significance
- **Power of the criterion**

The higher it is, the more likely it is to detect differences between the compared groups, and the greater statistical significance of the test criterion is. The larger power of the criterion is, the larger sample size is required

- Data variability
- Least expected treatment effect

What affects the sample size

- Level of significance
- Power of the criterion
- **Data variability**

When estimating sample size, it is often necessary to know the spread of the data, which is required to estimate the variance or the standard deviation. The bigger they are the larger sample size may be required

- Least expected treatment effect

What affects the sample size

- Level of significance
- Power of the criterion
- Data variability
- **Least expected treatment effect**

Treatment effect is the magnitude of the clinical benefit of the treatment, which is clinically important. It is often expressed through the difference in statistics: for example, through the difference between means, standard deviations or proportions

Difficulties

Variability is unknown, as the data has not been analyzed

The magnitude of treatment effect is unknown before the trial is conducted

Patients may be non-compliant to their treatment regimens

Patient's data may not be entered correctly, or patients may be lost to follow-up

Difficulties: Variability

- Use the data from similar published trials, from literature or from a pilot study
- Estimate the known min and max values of a parameter
- Estimate standard deviation as the difference between the max and min known values of the parameter, divided by 4

Difficulties: Treatment effect

- Try to determine direction of the effect and define its min and max values
- Consider several options for the possible effect, estimate the sample size for each of them and choose the most optimal one
- Find if it's possible to allocate a budget for the inclusion of several more patients, in order to observe the effect, that can't be seen at a current stage of a clinical trial

Difficulties: Treatment effect (cont.)

- Assess whether the cost of including new patients is worthwhile to detect a difference between groups if at the current stage of a trial either the effect of the treatment is already present, or there is no effect at all
- Do the opposite, and find out what effect will be unreasonable for detection

Difficulties: Non-compliance

Recalculate sample size to include non-compliant patients in treatment and control groups

$$N' = \frac{N}{(1 - P_c - P_t)^2}$$

Difficulties: Losses to follow-up

Recalculate sample size to add percent of patients, that will not be included into the final analysis because of incorrect data or loss to follow-up

$$N' = \frac{N}{1 - q}$$

Tools to estimate the sample size

- SAS: PROC POWER
- SAS: PROC GLMPOWER
- R: PWR package
- R: powerSurvEpi package
- User defined functions in SAS

1. PROC GLMPower in SAS: difference between means

The effect of Vitamin D compared to placebo on the prevention of neonatal hypocalcaemia is examined on pregnant women

MAIN EFFICACY PARAMETER	Serum calcium level
MEAN	9.0mg/100ml
STANDARD DEV	1.8 mg/100ml
TREATMENT EFFECT	Increase of 0.5 mg/100ml
POWER	95%
LEVEL OF SIGNIFICANCE	5%

1. PROC GLMPower in SAS: difference between means

```
data oneway;  
    level = "a1";  
    meanest = 9; output;  
    level = "a2";  
    meanest = 9.5; output;  
run;  
proc glmpower data=oneway;  
    class level;  
    model meanest = level;  
    power  
    stddev = 1.8  
    alpha = 0.05  
    ntotal = .  
    power = .95;  
run;
```

The SAS System
The GLMPower Procedure

Computed N Total		
Error DF	Actual Power	N Total
674	0.950	676

2. PROC POWER in SAS: time-to-event data

The influence of HDL-Plus on the risk of a heart attack is studied. 20% of patients are expected to suffer a heart attack over the course of the 5 years of follow-up. Patients taking HDL-Plus can expect their risk of a heart attack to decrease to approximately 15%

MAIN EFFICACY PARAMETER	Risk of a heart attack
FOLLOW-UP TIME	5 years
EVENT RATE IN CONTROL GROUP	20%
TREATMENT EFFECT	Decrease of rate to 15%
POWER	80%
LEVEL OF SIGNIFICANCE	5%

2. PROC POWER in SAS: time-to-event data

```
proc power;
  twosamplesurvival
  test = logrank
  curve("Control")    =(0 5) : (1 0.8)
  curve("Treatment")=(0 5) : (1 0.85)
  refsurvival = "Control"
  accrualtime = 2.5
  followuptime = 2.5
  hazardratio = 1.373
  alpha = 0.05
  sides = 2
  ntotal = .
  power = 0.8;
run;
```

The SAS System
The POWER Procedure
Log-Rank Test for Two Survival Curves

Computed N Total	
Actual Power	N Total
0.800	1772

3. User defined functions in SAS: time-to-event data

Formula for estimation of sample size:

$$N = \frac{1}{\pi_c + \pi_t} \left(\frac{\theta + 1}{\theta - 1} \right)^2 (Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2$$

π_t and π_c are the probabilities of the event to happen of a patient in treatment and control groups respectively during a trial.

$\theta = \frac{\log(1-\pi_c)}{\log(1-\pi_t)}$ is a relative risk of the event occurrence, or hazard ratio.

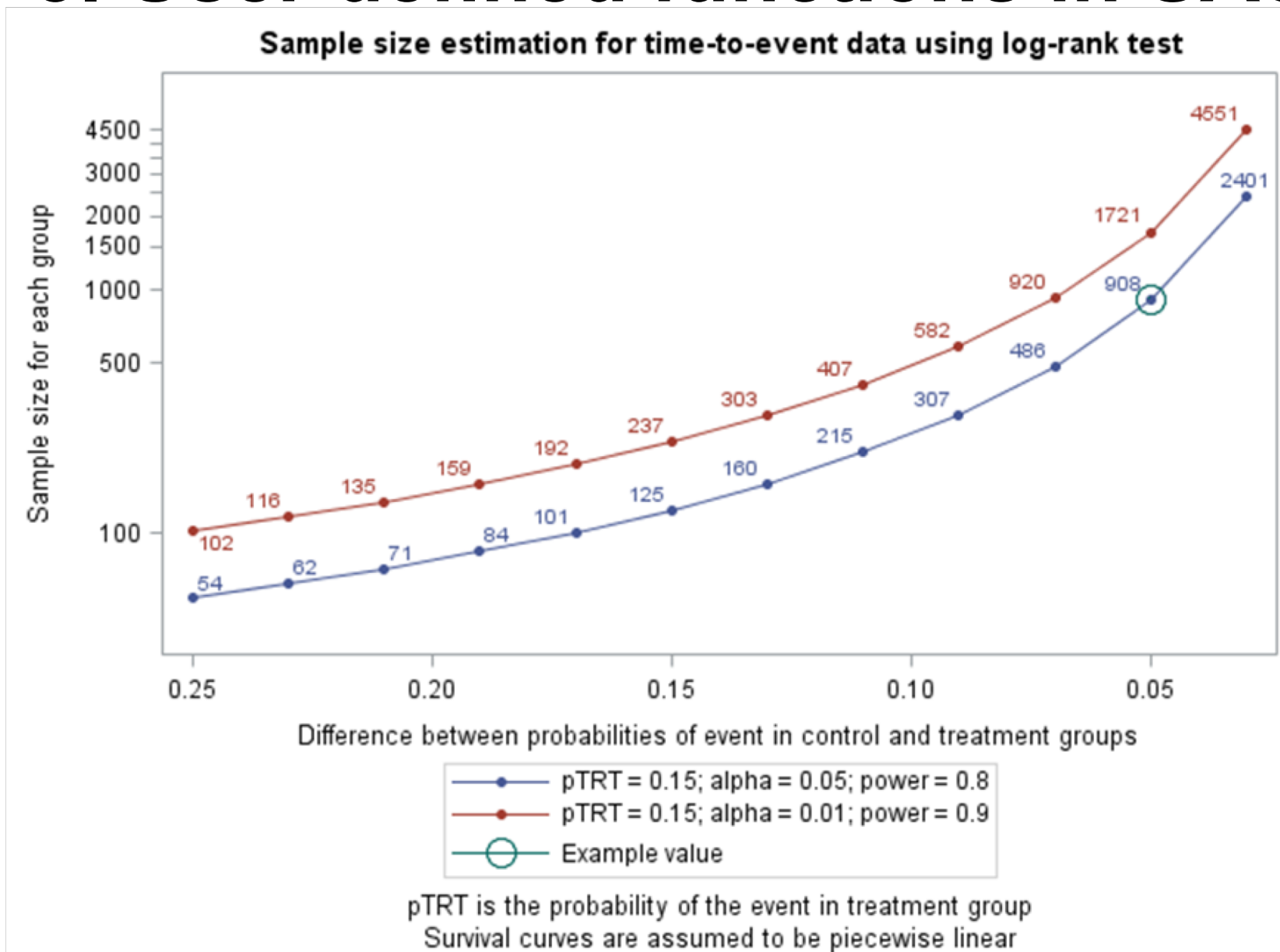
3. User defined functions in SAS: time-to-event data

```
proc fcmp outlib = work.mysubs.myfunc;
  function twosamplelogrank(piT, piC, alpha, power);
    *Simple checks to make sure all parameters are valid;
    if 0 ge piC ge 1 or 0 ge piT ge 1 then do;
      put "%str(ER)ROR: check sample parameters input! Must be between 0 and 1!";
      return;
    end;
    if 0 ge alpha ge 1 or 0 ge power ge 1 then do;
      put "%str(ER)ROR: check parameters alpha and power input! Must be between 0
and 1!";
      return;
    end;

    theta = log(1 - piC) / log(1 - piT);
    N = ((theta + 1)**2)*(probit(1 - alpha/2) + probit(power))**2 / ( (piC +
piT)*(theta - 1)**2 );

    return(ceil(N));
  endsub;
run;
```

3. User defined functions in SAS:



4. PWR package in R: difference between proportions

The efficacy of corticosteroid injections compared to physiotherapy in treating a painful rigid shoulder is examined. Success means that 40% of patients in the group where treatment is less effective have a response

MAIN EFFICACY PARAMETER	Risk of a heart attack
RATE IN TREATMENT GROUP	65%
RATE IN CONTROL GROUP	40%
TREATMENT EFFECT	Difference by 25% between groups
POWER	80%
LEVEL OF SIGNIFICANCE	5%

4. PWR package in R: difference between proportions

```
install.packages("pwr")
library(pwr)

effect <- ES.h(0.4, 0.65)

pwr.2p.test(h = effect,
            n = NULL,
            sig.level = 0.05,
            power = 0.8,
            alternative = "two.sided")
```

```
## Difference of proportion
## power calculation for
## binomial distribution
## (arcsine transformation)
##
##          h = 0.5060506
##          n = 61.29835
##      sig.level = 0.05
##          power = 0.8
##      alternative = two.sided
##
## NOTE: same sample sizes
```

Do results match?

	SAS		R		
	PROC GLMPOWER	PROC POWER	PWR package	powerSurvEpi package	User defined formulas
Difference in means	676	676	676	-	674
Difference in proportions	-	124	124	-	124
Time-to-event data	-	1772	-	Linear 1816	Linear 1816 Exp 1730

Conclusions

PLAN: It is highly important to calculate the required sample size before a clinical trial starts, so that the trial will not become a waste of resources.

All aspects of the trial design must be taken into account for an accurate assessment

Conclusions

ACT: Many resources are available, such as procedures in SAS and R that may reflect the clinical trial model in detail.

The variety of these resources may help to check the results obtained



Thank you for your attention!

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