Demystifying

Sample Size Estimation

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Overview

- Underlying concepts
- Getting ready to estimate sample size
- Calculating sample size

Why estimate '*Sample Size*'?

- **Too small**
  - ✓Cannot find a real effect – waste of time/resources
  - ✓Leads to imprecision
- **Too large**
  - ✓Waste of resources
  - ✓Unethical

Determinants of sample size

1. Significance level
2. Power

Fixed

3. Effect size of intervention
4. Variability

Variable

Others: Event rate, one-sided vs. two-sided hypothesis, etc.

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Hypothesis testing: 4 possible outcomes

		TRUTH	
		Intervention **better** than control	Intervention **same** as control
STUDY FINDING	Intervention better than control	Correct	**α error (Type 1)**
	Intervention same as control	**β error (Type 2)**	Correct

Type I error (Alpha)

- Probability of obtaining a significant result by CHANCE (*false-positive)*
- Alpha=0.05 means investigator has set 5% probability that a significant difference will occur by chance

Alpha error & Sample size

To reduce alpha error (chance effect), INCREASE the sample size

Beta error & Power

- **Beta**
  - ✓Probability of NOT finding a difference when it actually exists (*false-negative)*
- **Power**
  - ✓Ability to detect a difference when it exists
  - ✓1-Beta
- Power=**80%** means investigator has set **80%** probability of detecting a treatment effect

Example

Radiologists

- Mean = 125
- SD = 15
- Sample size = 10

Orthopedicians

- Mean = 120
- SD = 15
- Sample size = 10

http://www.graphpad.com/quickcalcs/ttest1/?Format=SD

Example

Radiologists

- Mean = 125
- SD = 15
- Sample size = 100

Orthopedicians

- Mean = 120
- SD = 15
- Sample size = 100

http://www.graphpad.com/quickcalcs/ttest1/?Format=SD

Power and alpha

- **Not** always fixed
  - ✓Power : 80 to 90%
  - ✓Alpha : 0.05 to 0.01
- Potentially useful drug for a lethal disease

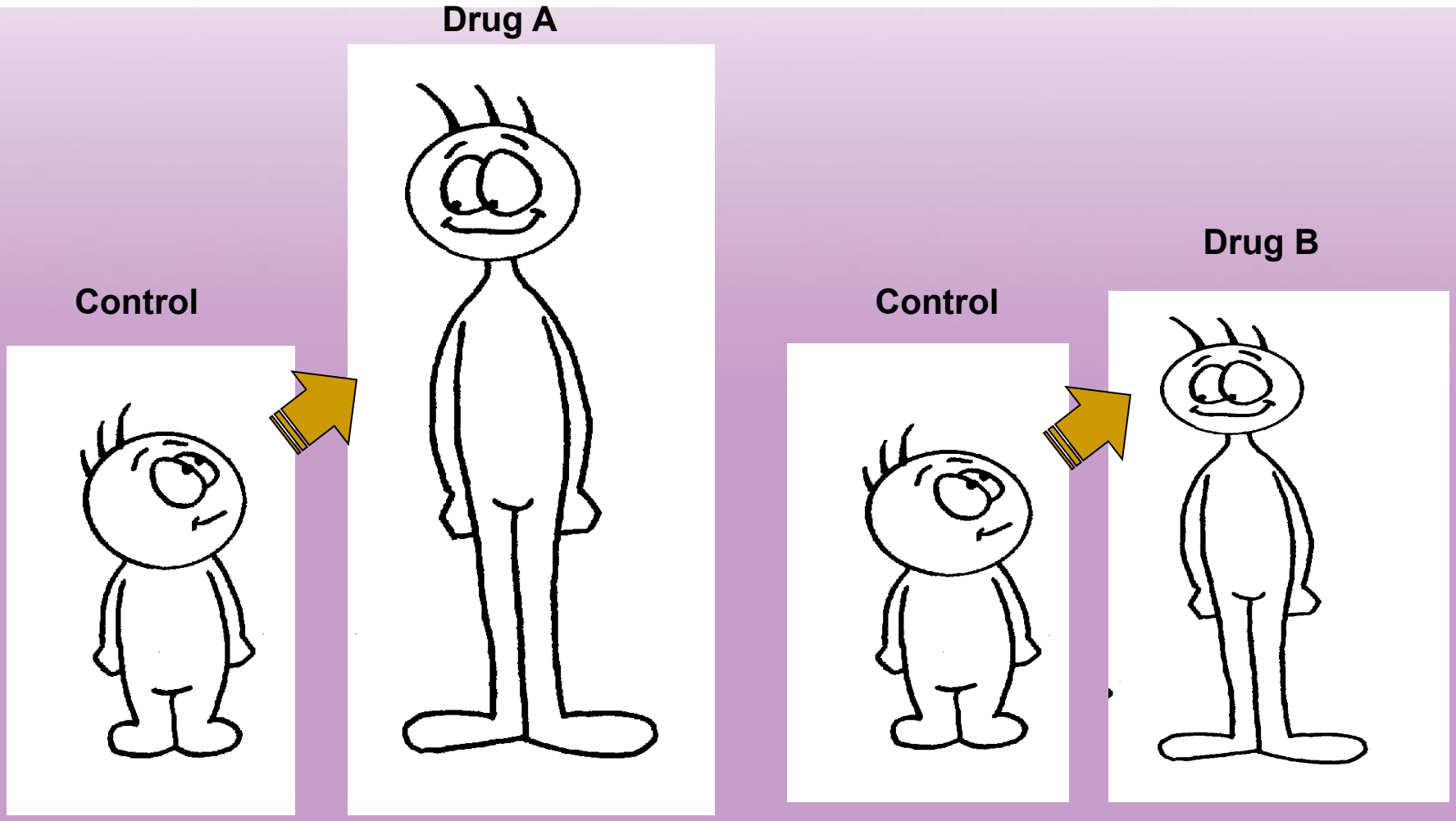
vs.

a drug with many side effects used for a common illness

Determinants of sample size

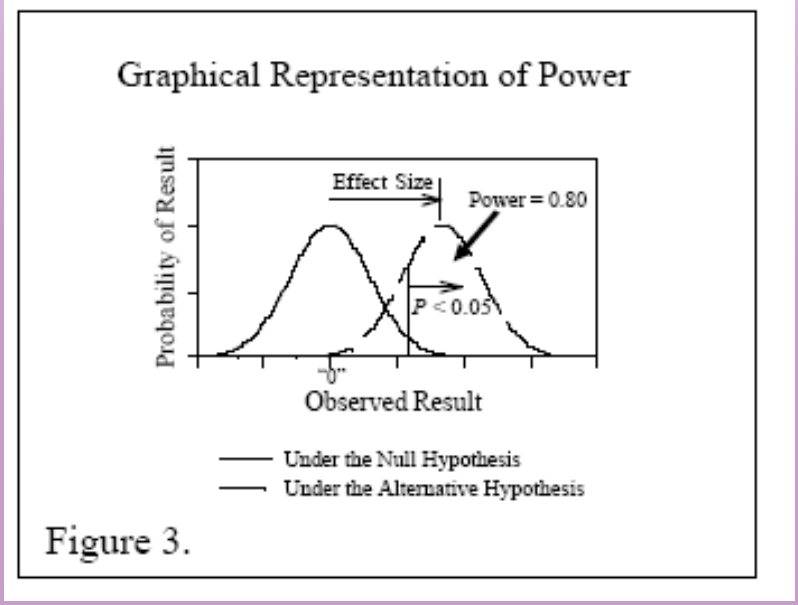
- Significance level
- Power
- Effect size of intervention
- Variability
- Others: Event rate, one-sided vs. two-sided hypothesis, etc.

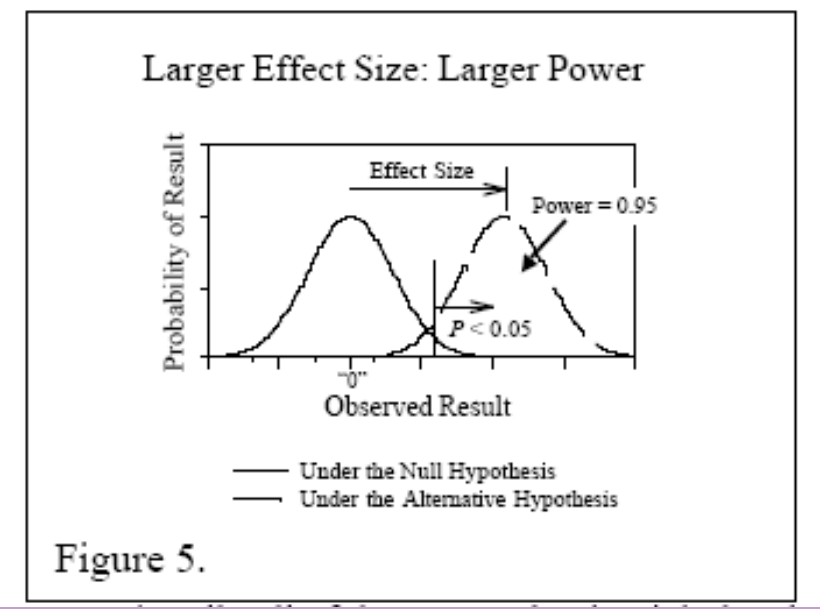
Effect size



Sample size would be less in ?

Effect size

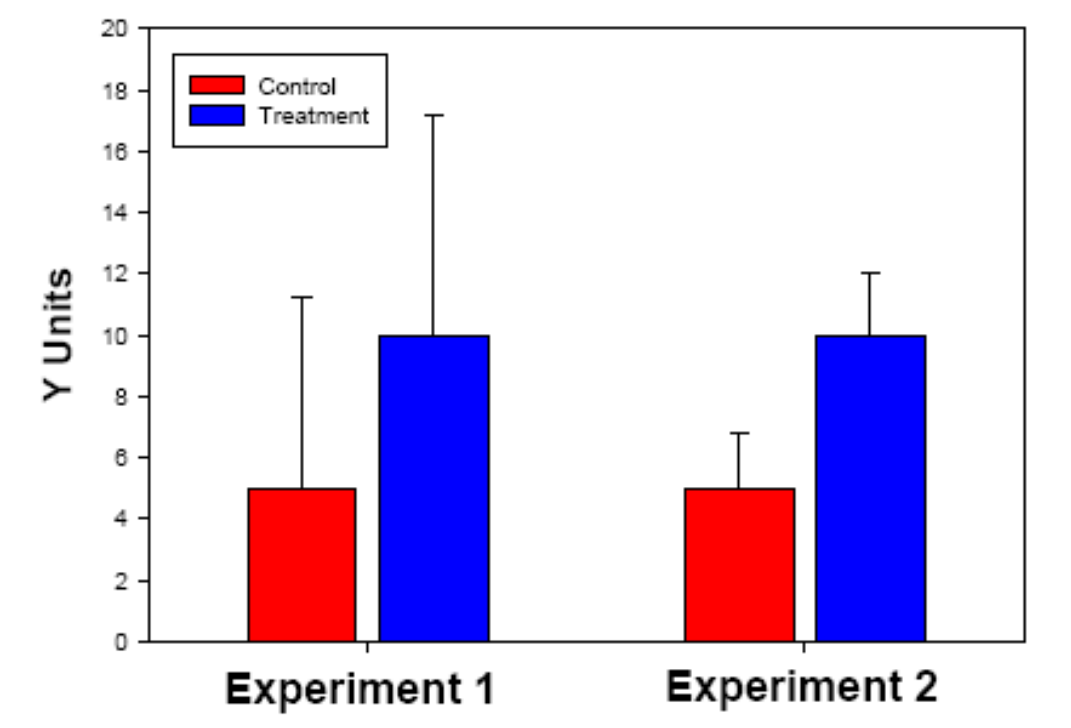




More the effect size, smaller the sample size

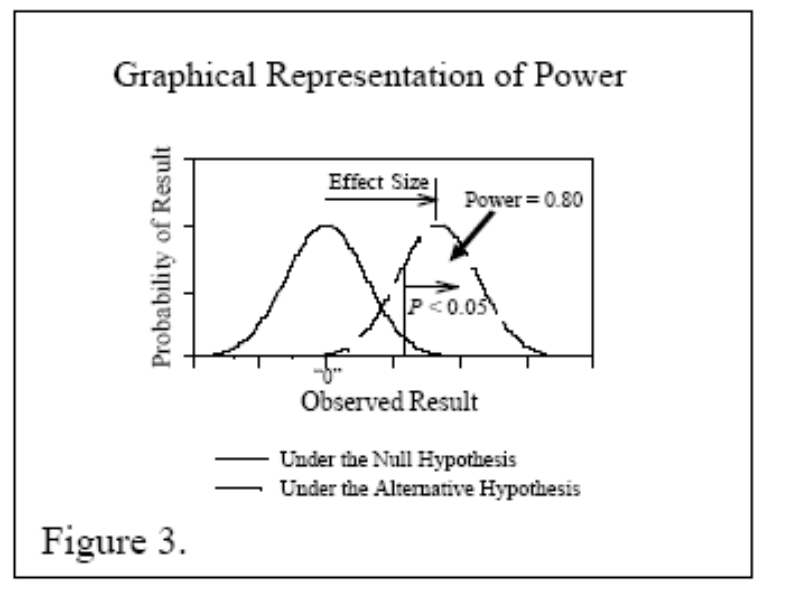
Note: With more power, you can detect an effect even with less sample size

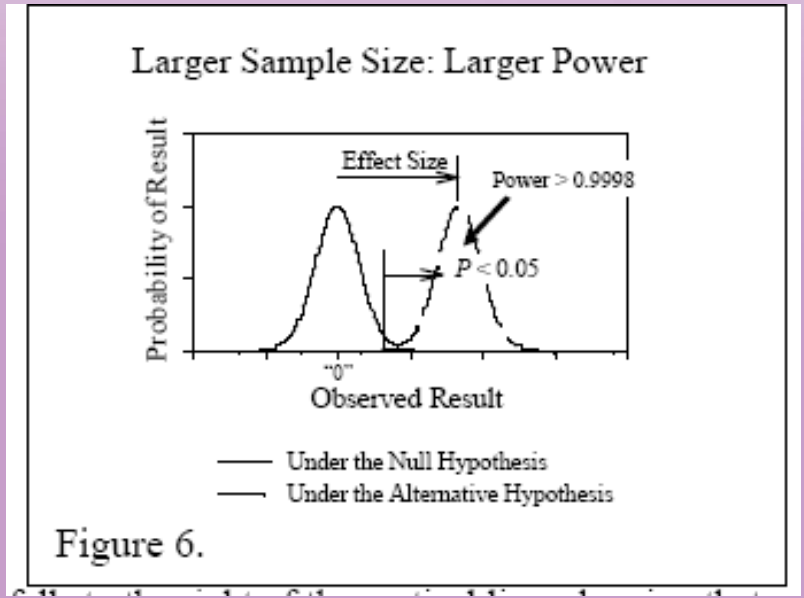
Variability



More the variability, less certain the treatment effect

Variability & sample size





To reduce variability, INCREASE the sample size

Summary

Determinant	Preferred	Sample size
Alpha (type I error)	Small	↑
Power	High	↑
Effect size	Small	↑
Variability	Less	↓

Effect size and variability

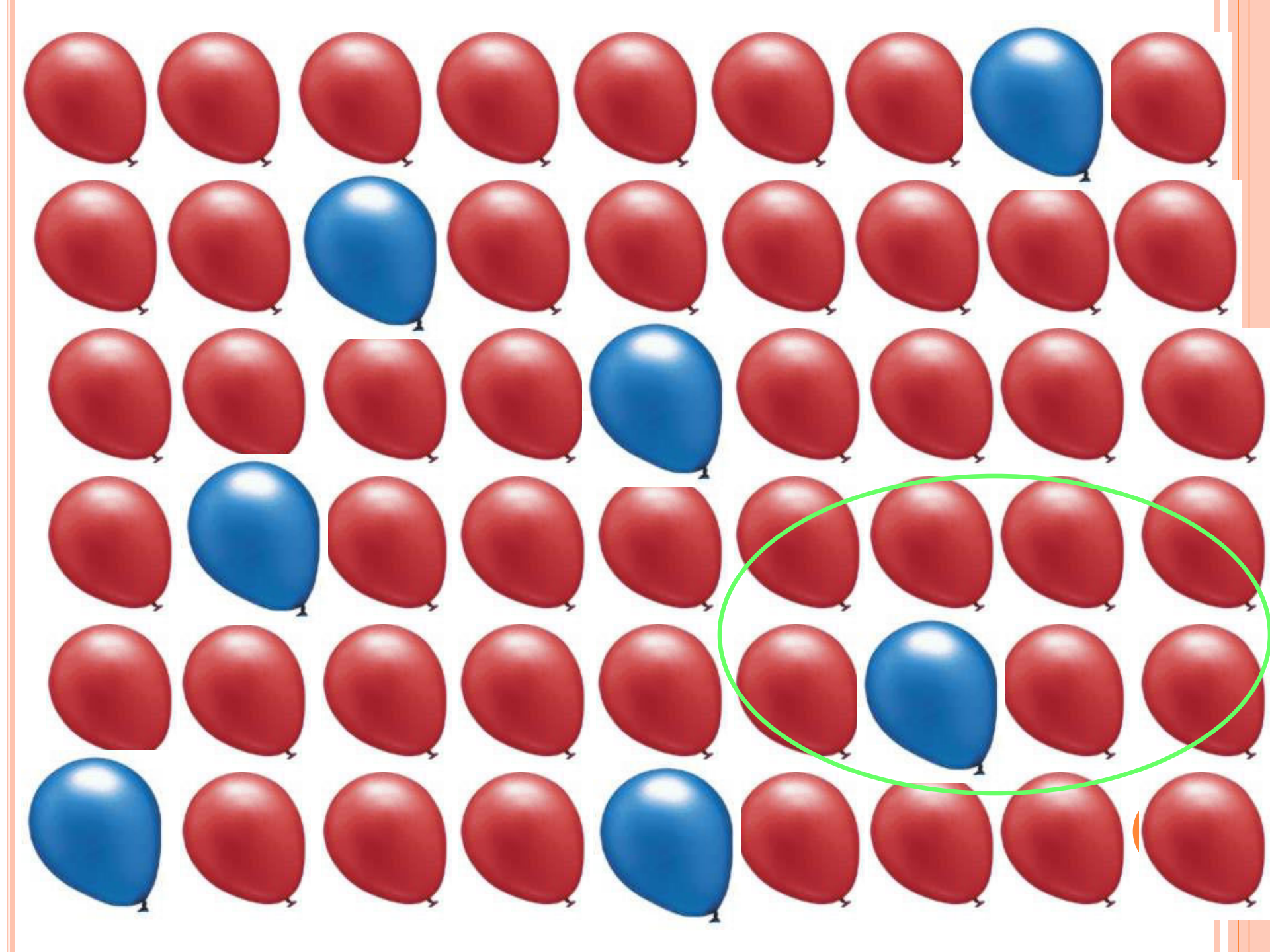
How to estimate?

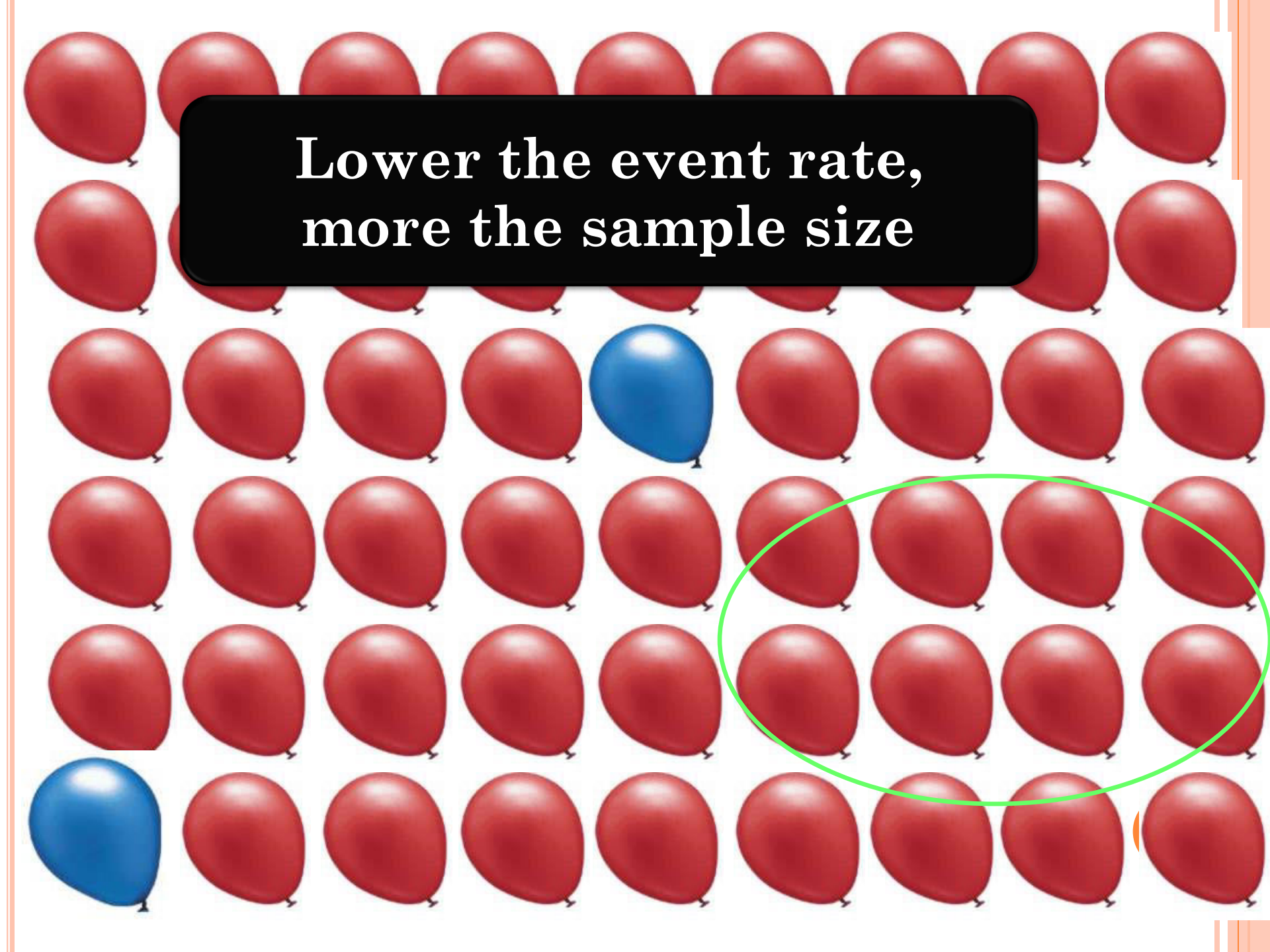
- Previous studies/animal experiments
- Pilot study
- Consultation with experts
- Educated guess

Determinants of sample size

- Significance level
- Power
- Variability
- Effect size of intervention
- Others: Event rate, one-sided vs. two-sided hypothesis, etc.

Event rate




Lower the event rate,
more the sample size

Sample size in prevalence studies

- E.g. cross-sectional survey
- One sample – NO effect size or power*
- Sample size determined by:
  1. Estimated proportion*
  2. Confidence (Alpha error)
  3. PRECISION

** Remember even in one sample, power comes into play if you are testing a hypothesis*

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Type of study designs

- cross-sectional
- cohort
- case-control
- experimental

Cross-sectional (survey)

Required information

1. anticipated population prop. (p)
2. type I error (5%)
3. precision (d)

An investigator seeks to estimate the proportion of children receiving vaccinations.

How many children must be studied if the estimate is to fall within 10% points of the true proportion with 95% confidence?

P = alpha=0.05 d= 10%

n = ?

Case-control study

Required information

1. At least 2 of the following:
   i. exposure rate in cases
   ii. exposure rate in controls
   iii. odds ratio
2. Probability of type 1 and 2 errors

A study is designed to compare the immunization rates in a group of TB cases compared to controls. Available information - 30% of controls are vaccinated, and we wish to have an 80% chance of detecting a significant difference at 5% level. An OR of 2 would be considered an important difference.

P_2 = Power = α = OR = 2.0

Cohort study/RCT

Required information

1. At least 2 of the following:
   i. Risk/incidence in exposed group
   ii. Risk/incidence in control group
   iii. Relative risk
2. Probability of two types of errors

A study to compare efficacy of drug A *vs.* placebo in leukemia patients. 40% of patients get recurrence with current treatment. If we wish to have 90% chance of detecting if new drug reduces it to 20% at 5% level of significance, what would be the *n*?

P_1 = P_2 = Power = $\alpha = 0.05$

RCT with continuous outcome variable

Required information

1. Mean of the outcome variable in group 1 = M1
2. Mean of the outcome variable in group 2 = M2
3. SD of the outcome variable in group 1 = σ1
4. SD of the outcome variable in group 2 = σ2
5. Probability of two types of errors

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Sample size calculators

- Epi-info
- PASS, Power&precision
- Stata
- Websites
  - http://www.epibiostat.ucsf.edu/dcr/
  - www.sealedenvelope.com
  - www.openepi.com

Rule of thumb

- formula for calculating the sample size in the case of a continuous variable:

  $15(SD/\text{difference in means})^2$

- For the examples we discussed, the sample size per group would be as follows:
- 1. Assuming the SD to be 1 and the expected difference in means to be 12 hrs, it would be 15 $(1/12)^2$ = **10** per group
- 2. Assuming the SD to be 24 and the expected difference to be 12 hrs, it would be 15 $(24/12)^2$ = **60** per group

Loss to follow-up

- Increase sample size by multiplying with

  [1/(1-expected drop-out rate)]
- e.g. if 20% drop-out rate and calculated sample size is 100, then enroll 125 subjects (100*1.25); [1/0.8=1.25]

Strategies to decrease sample size

- Use continuous variable instead of categorical variable
- Use paired measurement
- Use more precise variable
- Use a more common outcome

Resources

- Stephen B Hulley, Steven R Cummings. Designing Clinical Research : An epidemiologic approach, Williams and Wilkins, London 1988. page 139 – 150

- Stanley lemshow, David W Hoshmer, Janelle Klar, Adequacy of sample size in health studies. John Willey, and Sons. New York