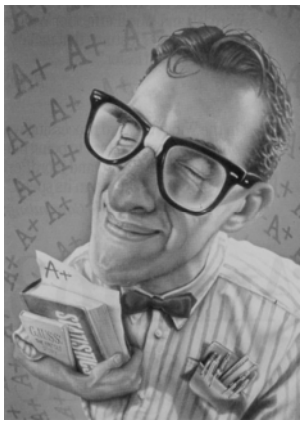
Sample Size Estimation

Phil Hahn
Queen's University

Give me more Power!

Power = $$$$

Power = 1 - β



How Big a Sample Do You Need?

- Fundamental research question
- Should be addressed after determining the primary objective and study design

How Big a Sample Do You Need?

- Too Few Patients
  - May fail to detect a clinically important difference
- Too Many
  - Involve extra patients
  - Therapy may have risks
  - Cost more

Review of 172 RCTs in NEJM and Lancet (1973-76)

- None mentioned a priori estimates of numbers required
- None discussed the magnitude of the clinically relevant difference

A. Ambros. Clinical Research 1978

How Big a Study?

- Objective: To increase survival by 5%
- New Cancer Treatment: 90%
- Standard Cancer Treatment: 85%
- We wish to have a 90% chance of finding this difference

How Big?

- 18
- 180
- 1,800
- 18,000
- 180,000

How Big?

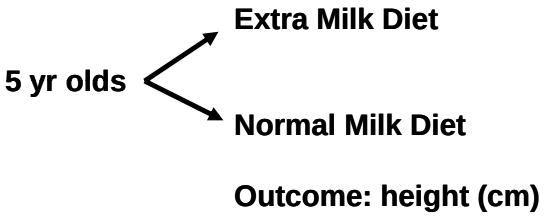
- 18
- 180
- **1,800**
- 18,000
- 180,000

Sample Size Statistics

Step 1. Define Primary Objective

- Too see if feeding milk to 5 year old kids enhances growth.

Step 2. Study Design



Step 3. Define clinically significant difference one wishes to detect

- Difference (Δ) of 0.5 cm

Step 4. Define degree of certainty of finding this difference

- Called beta (β) or type II error
- *The probability of NOT detecting a significant difference when there really is one.*
- Risk of a false-negative finding.
- Set at $\leq$ 20%

Type II Error

- Risk of declaring no significant difference in height between the milk diets when a difference really does exist.

Power of the Test

- Probability of detecting a predefined clinically significant difference.
- Power = (1 - β) = 1 - 20% = 80%

Step 5. Define significance level

- Called alpha (α) or type I error
- *The probability of detecting a significant difference when the treatments are really equally effective*
- Risk of a false-positive finding
- Set at 5%

Type I Error

- One has a 5% chance or 1 in 20 odds of declaring a significant difference between the milk diets when in fact they are really equal.
- We are willing to accept that 1 time out of 20 we will produce a false positive finding

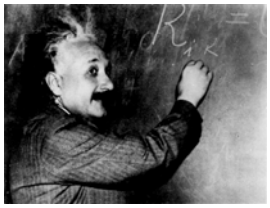
Statistical significance testing does not eliminate uncertainty, it merely quantifies it.

For the Milk Study

- Type I error (α) = 0.05
- Type II error (β) = 0.20
- Power = (1- β) = 0.80
- Clinically significant diff (Δ) = 0.5cm
- Measure of variation (SD) = 2.0 cm
  - Exists in literature or *"Guesstimate"*

Formula

$$N = \frac{2\,(SD)^2}{\Delta^2} \times f(\alpha, \beta)$$



Formula

$$N = \frac{2\,(SD)^2}{\Delta^2} \times f(\alpha, \beta)$$

Sample size:
Directly proportional to variation in measures.

Inversely proportional to the size of the clinically relevant difference.

Function Table

Alpha	Beta			
	0.05	0.10	0.20	0.50
0.10	10.8	8.6	6.2	2.7
0.05	13.0	10.5	7.9	3.8
0.02	15.8	13.0	10.0	5.4
0.01	17.8	14.9	11.7	6.6

Formula

$$N = \frac{2\,(SD)^2}{\Delta^2} \times f(\alpha, \beta)$$

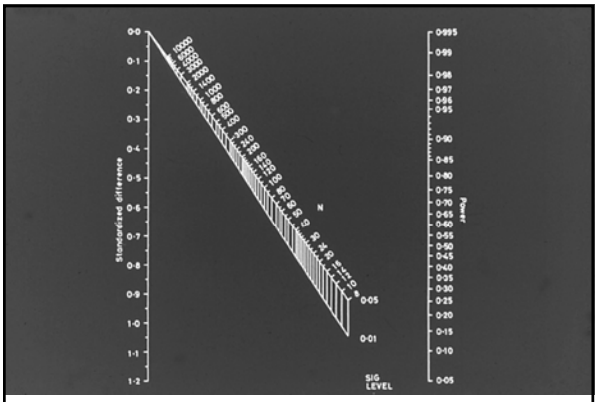
$$N = \frac{2\,(2)^2}{0.5^2} \times 7.9 = 252.8$$

(each group)

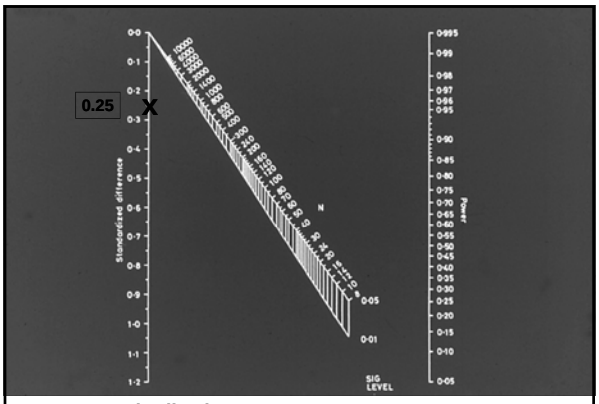
Simple Method

- **Nomogram**
- **Standardized difference**
  - **= smallest medically relevant diff / estimated standard deviation**
  - **= 0.5/2.0 = 0.25**

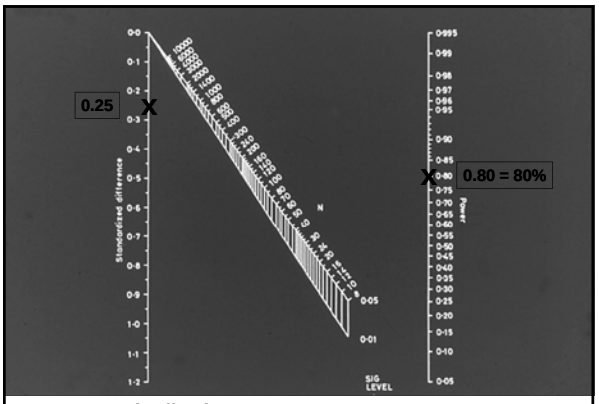
Douglas Altman. Statistics and ethics in medical research III: How large a sample? BMJ 1980;281:1336-8.



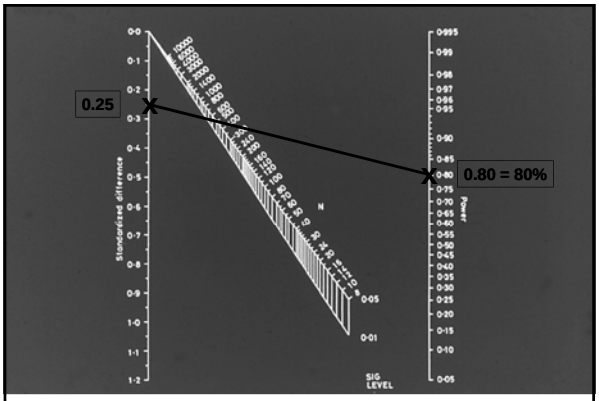
Standardized Difference **Power**



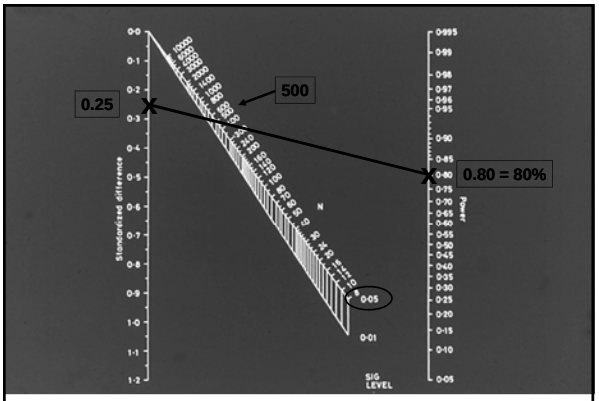
Standardized Difference | Power



Standardized Difference | Power



Standardized Difference | Power



Standardized Difference | Power

Simple Method

Assumptions:

1. 2 sample comparison only
2. Same number of subjects per group
3. Variable is a continuous measure that is normally distributed

Douglas Altman. BMJ (1980)

Sample Size Calculation

Nominal Data

Difference in Rates or Proportions

Study Objective

- To increase survival by 5% with a new cancer drug
- Std Drug: 85%
- New Drug: 90%
- Power = 90%

Formula

P1 = % survival (std) = 85%
P2 = % survival (new) = 90%

$$N = \frac{P1\,(100 - P1) + P2\,(100 - P2)}{(P2 - P1)^2} \times f(\alpha, \beta)$$

= 913.5 (each group)

= 1827 total

Clinical Significance

A very large study has the power to demonstrate statistical significance for very small, even clinically inconsequential differences.

Clinical Significance

A difference
to be a difference
must make a difference

Gertrude Stein (1874-1946)
American Writer in France

Portrait by Pablo Picasso 1906

Road Map

Do a sample size calculation
Before you start collecting data

↓

Collect data

↓

Perform statistical test
IF p value < 0.05, declare statistical significance

↓

Consider clinical significance
by looking at the size of the difference

Three Research Strategies

Nike Approach

Nike approach

- Get an idea
- *"Just do it!"*
- Small, negative trial
- Small, negative trial
- Small, negative trial
- Meta analysis

BOYCOTT NIKE

THE COCHRANE COLLABORATION®

Spider-Man Approach

Spider-Man approach

- Get an idea
- Estimate sample size
- TOO BIG!!!
- Network with colleagues
- Multi-centre Trial
- Positive Result

Schwarzenegger Approach

Schwarzenegger Approach

- Get an idea
- Estimate sample size
- TOO BIG!!!
- Terminate the project
- Save time & money