



De-Mystifying Sample Size to (Em)Power Your Study

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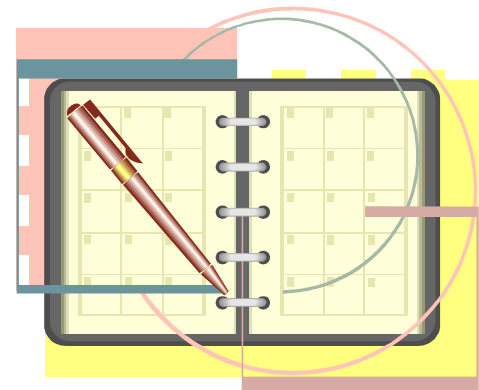
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Agenda

- Review of Sample Size and Power
- Regulatory Requirements
- Discussion of Endpoints
- Specifics
- Key Points
- Questions
- References



The larger the sample size (n) the more confident you can be that your sample mean is a good representation of the population mean. In other words, the " n " justifies the means.



What is Sample Size?

- The number of subjects in a trial?
- The number of subjects who finish a trial?
- The number of subjects I can find?

Answer: The number of subjects who are enrolled in a trial who will answer the primary trial question.

What does ICH E9 say?

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

Sample size should be:

- large enough to provide a reliable answer to the questions addressed
- determined by the primary objective of the trial (or otherwise justified)
- defined in the protocol and planned in advance

What does ICH E9 say?

The “usual” method:

- Specify the primary outcome variable based on indication
- Specify the test statistic
- Specify the null and alternative hypotheses
- Specify allowable Type I and Type II error
- Specify allowance for early withdrawal and protocol violations

Indications of Attendees

- Virology
- Gastroenterology
- Vaccines
- Dermatology
- Oncology
- Asthma and COPD
- Cardiovascular
- Analgesia and Anesthesia

Endpoints

Continuous	Categorical	Time to Event
Antibody counts	Seroconversion	Time to Seroconversion
Fecal Incontinence Score	20% Improvement in Score	Time to 20% Improvement
Pain Scores	Pain Reduction Response	Time to Pain Reduction
Tumor Size Reductions in Biomarkers	Tumor Response	Overall or Progression Free Survival
# of Exacerbations or Symptom Free Days	Symptom Free	Time to Exacerbation

Sample Size Formula

Two Sample Means (continuous)

$$n_1 = n_2 = \frac{2(z_{1-\alpha/2} + z_{1-\beta})^2 \sigma^2}{(\mu_2 - \mu_1)^2}$$

n_1, n_2 = sample size in arms 1 and 2

α = Allowable Type I Error (usually 5%)

β = Allowable Type II Error (usually 10 - 20%)

$1 - \beta$ = Power (usually 80-90%)

σ = Standard Deviation

$\mu_1 - \mu_2$ = Clinically Meaningful Difference in Means

Example: Blood Pressure

$$n_1 = n_2 = \frac{2(1.96 + 0.84)^2 20^2}{15^2}$$

= 28 subjects per group

$$\alpha = 0.05, \beta = 0.20$$

$$\sigma = 20 \text{ mm Hg}$$

$$\mu_1 - \mu_2 = 15 \text{ mm Hg}$$

$$z_{1-0.05/2} = 1.96, z_{1-0.20} = 0.84^*$$

*inverse normal distribution

Difference in Two Proportions (categorical)

$$n_1 = n_2 = \frac{2(z_{1-\alpha/2} + z_{1-\beta})^2 \sigma^2}{(\pi_2 - \pi_1)^2}$$

Where

$$\sigma^2 = \frac{1}{2} \{ \pi_1 (1 - \pi_1) + \pi_2 (1 - \pi_2) \}$$

π_1 = Proportion in group 1

π_2 = Proportion in group 2

$\pi_1 - \pi_2$ = Difference in Proportions

Example: Pain Relief Responder

$$\sigma^2 = \frac{1}{2} \{0.2(0.8) + 0.7(0.3)\} = 0.185$$

$$n_1 = n_2 = \frac{2(1.96 + 0.84)^2(0.185)}{(0.5)^2}$$

= 12 subjects per group

$$\alpha = 0.05, \beta = 0.20$$

$$z_{1-0.05/2} = 1.96, z_{1-0.20} = 0.84$$

$$\pi_1 = .20 \text{ (placebo)}$$

$$\pi_2 = .70 \text{ (active)}$$

Odds Ratio (categorical)

Can use same formula!

$$OR = \frac{\pi_1 / (1 - \pi_1)}{\pi_2 / (1 - \pi_2)}$$

$$\pi_1 = \frac{\pi_2 * OR}{1 + \pi_2 (OR - 1)}$$

- 1) Find π_1
- 2) Find σ^2
- 3) Find sample size

Difference in Two Hazard Rates (Time to event)

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{(\lambda_2 - \lambda_1)^2} [\sigma^2(\lambda_1) + \sigma^2(\lambda_2)]$$

Where

$$\sigma^2(\lambda_i) = \lambda_i^2 \left(1 + \frac{e^{-\lambda_i T} - e^{-\lambda_i(T-T_0)}}{\lambda_i T_0} \right)^{-1}$$

λ_1 = Hazard in group 1, λ_2 = Hazard in group 2

T = length of trial, T_0 = length of accrual

And σ^2 depends on λ_i

Example: Cancer Trial, Difference in Progression Rates

$$n = \frac{(1.96 + 0.84)^2}{(2 - 1.5)^2} [2.29 + 4.06]$$

=200 subjects per arm

$$\alpha = 0.05, \beta = 0.20$$

$$z_{1-0.05/2} = 1.96, z_{1-0.20} = 0.84$$

$$\lambda_1 = 2 \text{ (standard of care)}$$

$$\lambda_2 = 1.5 \text{ (study treatment)}$$

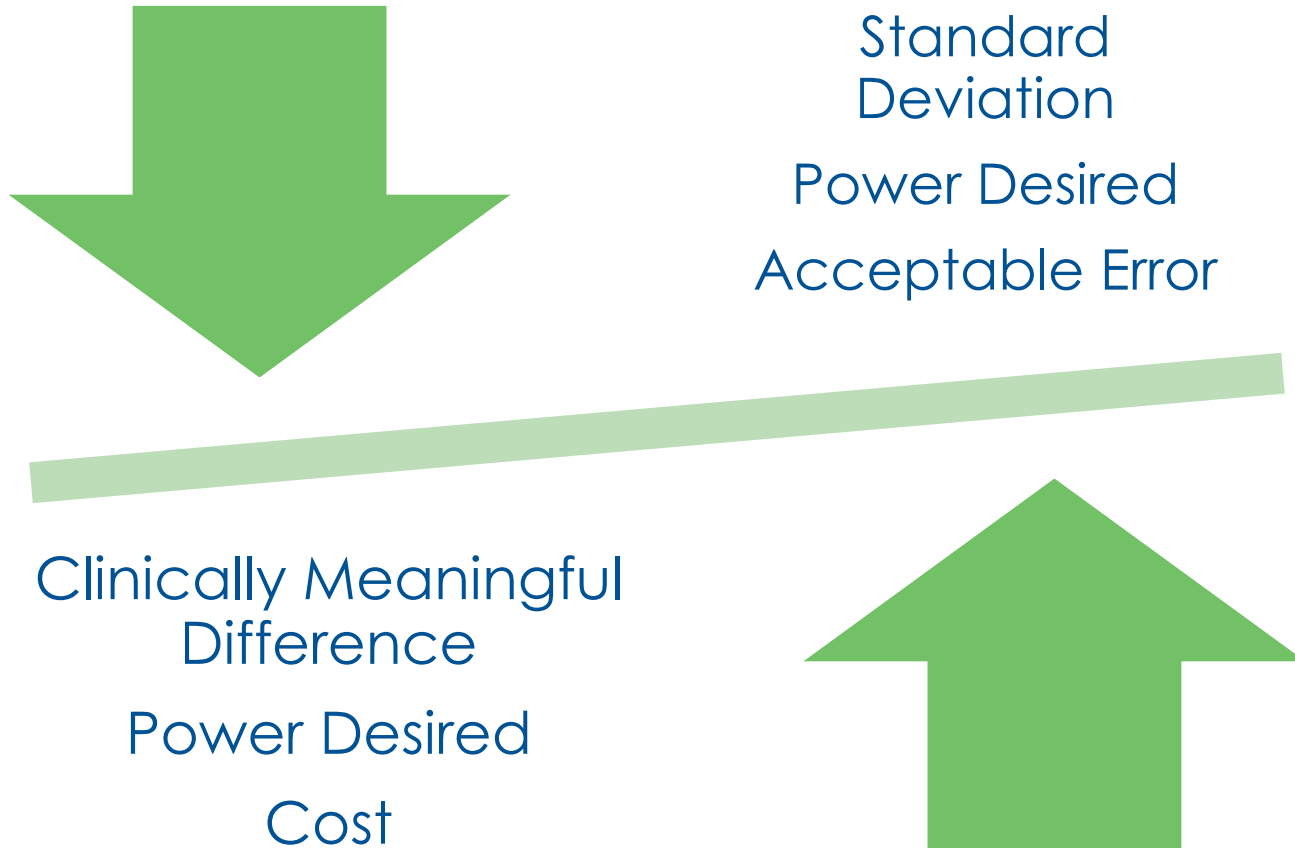
Example: <http://hansheng.gsm.pku.edu.cn/pdf/2007/surv.pdf>

How do we do this in real life?

I do NOT hand calculate sample sizes

- SAS®
- Nquery (Demo)
 - <http://www.statistical-solutions-software.com/nquery-advisor-nterim/>
- PASS (free trial)
 - <http://www.ncss.com/software/pass/>

Sample Size and Power



Remember!

- The lower the allowable error, the bigger the sample size
- The higher the power, the bigger the sample size
- The bigger the standard deviation, the bigger the sample size
- The bigger the clinically meaningful difference, the smaller the sample size

Question and Answer Session



References

ICH E9

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

Sample Size Estimation in Clinical Trials

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148614/>

Sample Size Calculation in Clinical Trials

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933537/>

Sample Size Calculation for Comparing Time to Event Data

<http://hansheng.gsm.pku.edu.cn/pdf/2007/surv.pdf>