Sample Size and Power

Chapter 22, 3rd Edition
Chapter 15, 2nd Edition

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Disclaimer

- **This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.**

Why care about sample size and power?

Power = probability of getting a statistically significant result, when in fact there is a 'clinically' meaningful difference (unknown to us)

By definition, studies with low power are less likely to produce statistically significant results, even when a clinically meaningful effect does exist

Lack of statistical significance does not prove that there is no treatment effect, but instead may be a consequence of small sample size (i.e. low power)

Therefore, it is important to have enough power and an adequate sample size

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Objectives

- Calculate changes in sample size based on changes in the difference of interest, variance, or number of study arms
- Understand intuition behind power calculations
- Recognize sample size formulas for the tests
- Learn tips for getting through an IRB

Take Away Message

- Get some input from a statistician
  - This part of the design is vital and mistakes can be costly!
- Take all calculations with a few grains of salt
  - "Fudge factor" is important!
- Round UP, never down (ceiling)
  - Up means 10.01 becomes 11
- Analysis Follows Design

Take Home: What you need for N

- What difference is scientifically important in units – *thought, discussion*
  - 0.01 inches?
  - 10 mm Hg in systolic blood pressure?
- How variable are the measurements (accuracy)? – *Pilot!*
  - Plastic ruler, Micrometer, Caliper

Sample Size

- Difference (effect) to be detected (δ)
- Variation in the outcome (σ^2)
- Significance level (α)
  - One-tailed vs. two-tailed tests
- Power
- Equal/unequal arms
- Superiority or equivalence or non-inferiority

Vocabulary

- Follow-up period
  - How long a participant is followed
- Censored
  - Participant is no longer followed
    - Incomplete follow-up (common)
    - Administratively censored (end of study)
- More in my next lecture

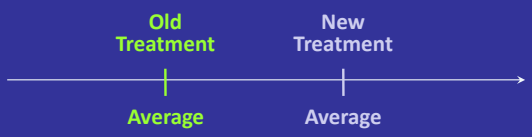
Question

Without ____?____ , there is no need for Statistics

Answer

Without *variability*, there is no need for Statistics

Variability



Variability

Variability

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Variability

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Outline

- **Power**
- Basic Sample Size Information
- Examples (see text for more)
- Changes to the basic formula
- Multiple comparisons
- Poor proposal sample size statements
- Conclusion and Resources

Power Depends on Sample Size

- Power = 1-β = P(reject H_0 | H_1 true)
  - "Probability of rejecting the null hypothesis if the alternative hypothesis is true."
- More subjects ➔ higher power

Power is Affected by…..

- Variation in the outcome (σ^2)
  - ↓ σ^2 → power ↑
- Significance level (α)
  - ↑ α → power ↑
- Difference (effect) to be detected (δ)
  - ↑ δ → power ↑
- One-tailed vs. two-tailed tests
  - Power is greater in one-tailed tests than in comparable two-tailed tests

Power Changes

- 2n = 32, 2 sample test, 81% power, δ=2, σ = 2, α = 0.05, 2-sided test
- Variance/Standard deviation
  - σ: 2 → 1 Power: 81% → 99.99%
  - σ: 2 → 3 Power: 81% → 47%
- Significance level (α)
  - α : 0.05 → 0.01 Power: 81% → 69%
  - α : 0.05 → 0.10 Power: 81% → 94%

Power Changes

- 2n = 32, 2 sample test, 81% power, δ=2, σ = 2, α = 0.05, 2-sided test
- Difference to be detected (δ)
  - δ : 2 → 1 Power: 81% → 29%
  - δ : 2 → 3 Power: 81% → 99%
- Sample size (n)
  - n: 32 → 64 Power: 81% → 98%
  - n: 32 → 28 Power: 81% → 75%
- Two-tailed vs. One-tailed tests
  - Power: 81% → 88%

Power should be….?

- Phase III: industry minimum = 80%
- Some say Type I error = Type II error
- Many large "definitive" studies have power around 99.9%
- Omics studies: aim for high power because Type II error a bear!

Power Formula

- Depends on study design
- Not hard, but can be VERY algebra intensive
- May want to use a computer program or statistician

Outline

- ✓Power
- ➢Basic Sample Size Information
- Examples (see text for more)
- Changes to the basic formula
- Multiple comparisons
- Rejected sample size statements
- Conclusion and Resources

Basic Sample Size

- Changes in the difference of interest have HUGE impacts on sample size
  - 20 point difference → 25 patients/group
  - 10 point difference → 100 patients/group
  - 5 point difference → 400 patients/group
- Changes in difference to be detected, α, β, σ, number of samples, if it is a 1- or 2-sided test can all have a large impact on your sample size calculation

Basic 2-Arm Study's TOTAL Sample Size = $2N = \frac{4(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2}$

Basic Sample Size Information

- What to think about before talking to a statistician
- What information to take to a statistician
  - In addition to the background to the project

Nonrandomized?

- Non-randomized studies looking for differences or associations
  - Require larger sample to allow adjustment for confounding factors
- Absolute sample size is of interest
  - Surveys sometimes take % of population approach

Comments

- Study's primary outcome
  - Basis for sample size calculation
  - Secondary outcome variables considered important? Make sure sample size is sufficient
- Increase the 'real' sample size to reflect loss to follow up, expected response rate, lack of compliance, etc.
  - Make the link between the calculation and increase
- Always round up
  - Sample size = 10.01; need 11 people

Sample Size in Clinical Trials

- Two groups
- Continuous outcome
- Mean difference
- Similar ideas hold for other outcomes

Sample Size Formula Information

- Variables of interest
  - type of data e.g. continuous, categorical
- Desired power
- Desired significance level
- Effect/difference of clinical importance
- Standard deviations of continuous outcome variables
- One or two-sided tests

Sample Size & Data Structure

- Paired data
- Repeated measures
- Groups of equal sizes
- Hierarchical or nested data
- Biomarkers
- Validity (of what) studies

Sample Size & Study Design

- Randomized controlled trial (RCT)
  - Block/stratified-block randomized trial
  - Cluster randomized (etc)
- Equivalence, non-inferiority, superiority trial
- Non-randomized intervention study
- Observational study
- Prevalence study
- Measuring sensitivity and specificity

Outline

- ✓Power
- ✓Basic sample size information
- ➢Examples (see text for more)
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- Multiple comparisons
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How many humans do I need? Short Helpful Hints

- Not about power, about stability of estimates
- 15/arm minimum: good rule of thumb for early studies
  - 12-15 gives somewhat stable variance, sometimes
  - If using Bayesian analysis techniques at least 70/arm
- If n < 20-30, check t-distribution
- Minimum 10 participants/variable
  - Maybe 100 per variable

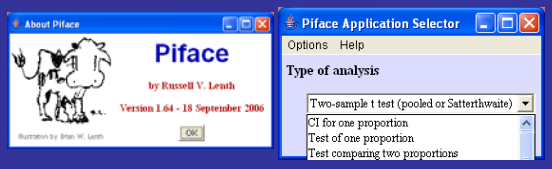
Live Statistical Consult!

- Sample size/Power calculation: cholesterol in hypertensive men example (Hypothesis Testing lecture)
- Choose your study design
  - Data on 25 hypertensive men (mean 220, s=38.6)
  - 20-74 year old male population: mean serum cholesterol is 211 mg/ml with a standard deviation of 46 mg/ml

Example

- Calculate power with the numbers given
- What is the power to see a 9 point difference in mean cholesterol with 25 people in
  - Was it a single sample or 2 sample example?

Sample Size Rulers



JAVA Sample Size

Put in 1-Sample Example #s

- 1 arm, t-test
- Sigma (sd) = 38.6
- True difference of means = 220-211=9
- n=25
- 2 sided (tailed) alpha = 0.05
  - Power=XXXX
- 90% power
  - Solve for sample size n=XXXX

Move the Values Around

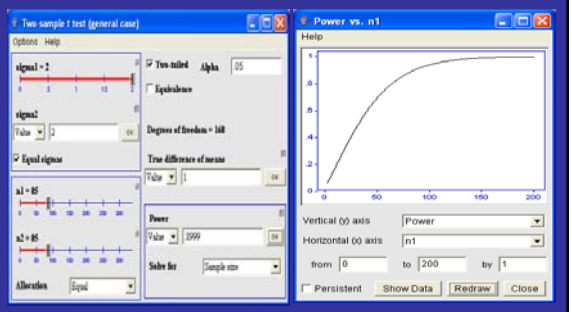
- Sigma (standard deviation, sd)
- Difference between the means

Different Study

Put in 2-Sample Example #s

- 2 arms, t-test
- Equal sigma (sd) in each arm = 2
- 2 sided (tailed) alpha = 0.05
- True difference of means = 1
- 90% power
- Solve for sample size

Keep Clicking "OK" Buttons



Phase I: Dose Escalation

- Dose limiting toxicity (DLT) must be defined
- Decide a few dose levels (e.g. 4)
- At least three patients will be treated on each dose level (cohort)
- Not a power or sample size calculation issue

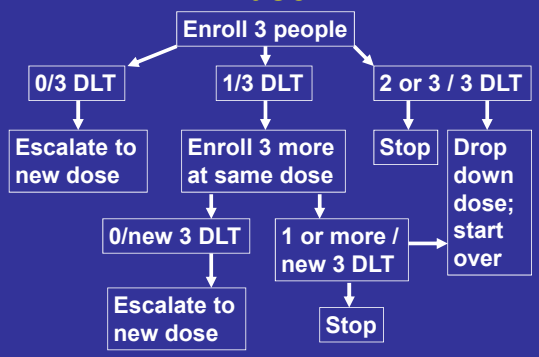
Phase I (Old Way)

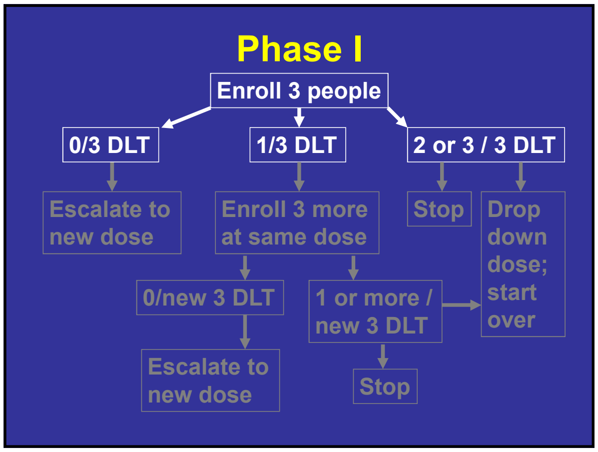
- Enroll 3 patients
- If 0 out of 3 patients develop DLT
  - Escalate to new dose
- If DLT is observed in 1 of 3 patients
  - Expand cohort to 6
  - Escalate if 0 out of the 3 new patients do not develop DLT (i.e. 1/6 at that dose develop DLT)

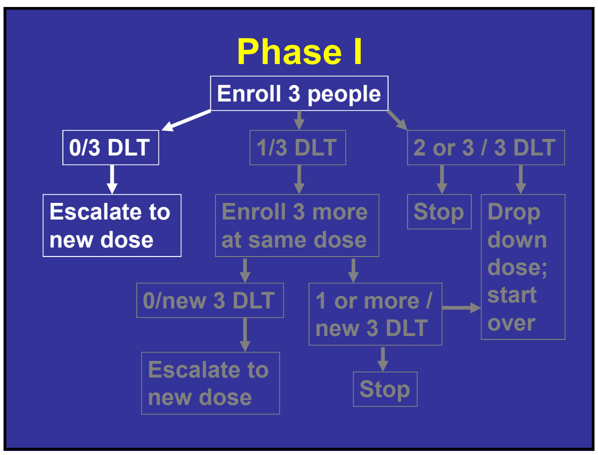
Phase I (cont.)

- Maximum Tolerated Dose (MTD)
  - Dose level immediately below the level at which ≥2 patients in a cohort of 3 to 6 patients experienced a DLT
- Usually go for "safe dose"
  - MTD or a maximum dosage that is pre-specified in the protocol

Phase I




Phase I
Enroll 3 people
0/3 DLT
1/3 DLT
2 or 3 / 3 DLT
Escalate to new dose
Enroll 3 more at same dose
Stop
Drop down dose; start over
0/new 3 DLT
1 or more / new 3 DLT
Escalate to new dose
Stop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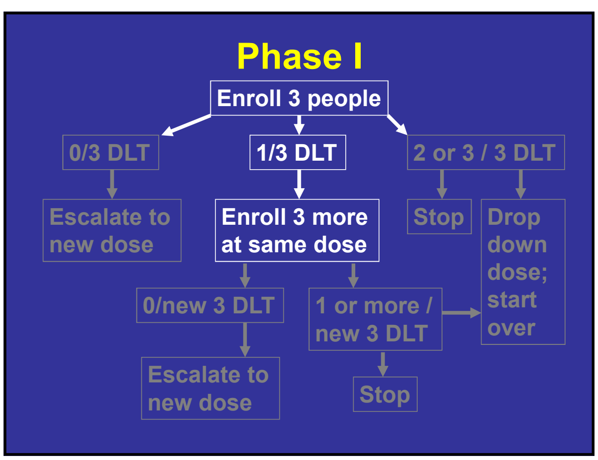
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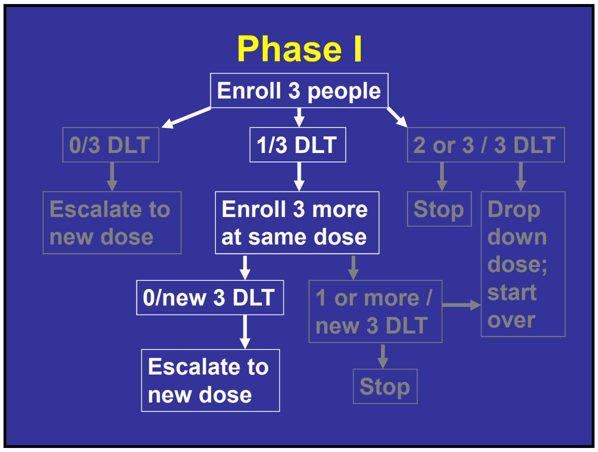
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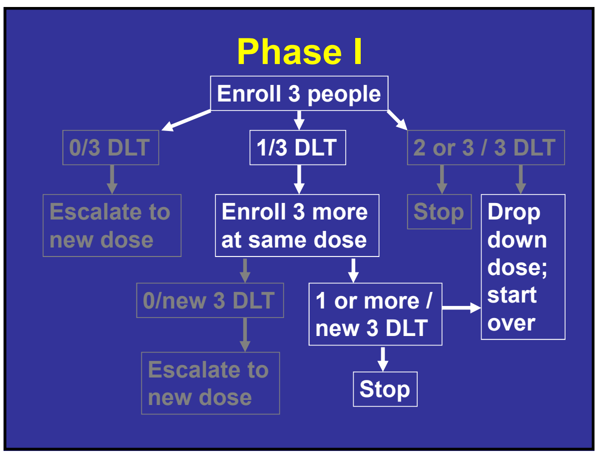
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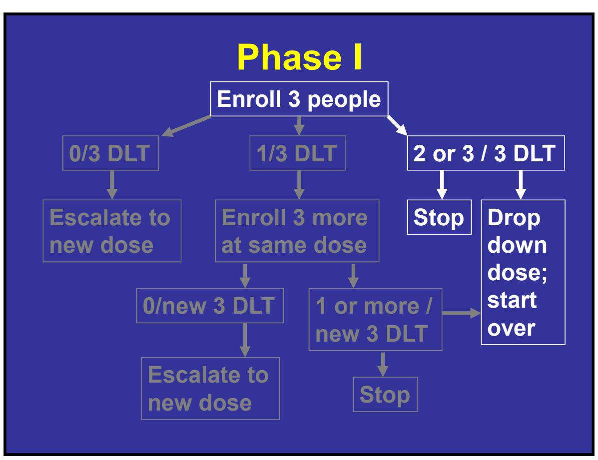
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0/3 DLT
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Escalate to new dose
Enroll 3 more at same dose
Stop
Drop down dose; start over
0/new 3 DLT
1 or more / new 3 DLT
Escalate to new dose
Stop

Number of pts with DLT	Decision
0/3	Escalate one level
1/3	Enroll 3 more at current level
0/3 + 0/3 *(To get here a de-escalation rule must have been applied at the next higher dose level)*	**STOP** and choose current level as MTD
1/3 + 0/3	Escalate one level *(unless a de-escalation rule was applied at next higher level, in which case choose current level as MTD)*
1/3 + {1/3* or 2/3 or 3/3}	**STOP*** and choose previous level as MTD *(unless previous level has only 3 patients, in which case treat 3 more at previous level)*
2/3 or 3/3	**STOP** and choose previous level as MTD *(unless previous level has only 3 patients, in which case treat 3 more at previous level)*

Phase I Note

- ***Implicitly targets a dose with Pr (Toxicity) ≤ 0.17; if at 1/3+1/3 decide *current* level is MTD then the Pr (Toxicity) ≤ 0.33**
- **Entry of patients to a new dose level does not occur until all patients in the previous level are beyond a certain time frame where you look for toxicity**
- **Not a power or sample size calculation issue**

Phase I

- **MANY new methods**
- **Several randomize to multiple arms**
- **Several have control arms**
- **Several have 6-15 people per arm**

Phase II Designs

- Screening of new therapies
- Not to prove 'final' efficacy, usually
  - Efficacy based on surrogate outcome
- Sufficient activity to be tested in a randomized study
- Issues of safety still important
- Small number of patients (still may be in the hundreds total, but maybe less than 100/arm)

Phase II Design Problems

- Might be unblinded or single blinded treatment
- Placebo effect
- Investigator bias
- Regression to the mean

Phase II: Two-Stage Optimal Design

- Seek to rule out undesirably low response probability
  - E.g. only 20% respond (p0=0.20)
- Seek to rule out p0 in favor of p1; shows "useful" activity
  - E.g. 40% are stable (p1=0.40)

Phase II Example: Two-Stage Optimal Design

- Single arm, two stage, using an optimal design & predefined response
- Rule out response probability of 20% (H_0: p=0.20)
- Level that demonstrates useful activity is 40% (H_1:p=0.40)
- α = 0.10, β = 0.10

Two-Stage Optimal Design

- Let α = 0.1 (10% probability of accepting a poor agent)
- Let β = 0.1 (10% probability of rejecting a good agent)
- Charts in Simon (1989) paper with different p1 – p0 amounts and varying α and β values

Table from Simon (1989)

Table 1 Designs for $p_1 - p_0 = 0.20$*

		Optimal Design				Minimax Design			
		Reject Drug if Response Rate				Reject Drug if Response Rate			
p_0	p_1	$\leq r_1/n_1$	$\leq r/n$	$EN(p_0)$	$PET(p_0)$	$\leq r_1/n_1$	$\leq r/n$	$EN(p_0)$	$PET(p_0)$
0.05	0.25	0/9	2/24	14.5	0.63	0/13	2/20	16.4	0.51
		0/9	2/17	12.0	0.63	0/12	2/16	13.8	0.54
		0/9	3/30	16.8	0.63	0/15	3/25	20.4	0.46
0.10	0.30	1/12	5/35	19.8	0.65	1/16	4/25	20.4	0.51
		1/10	5/29	15.0	0.74	1/15	5/25	19.5	0.55
		2/18	6/35	22.5	0.71	2/22	6/33	26.2	0.62
0.20	0.40	3/17	10/37	26.0	0.55	3/19	10/36	28.3	0.46
		3/13	12/43	20.6	0.75	4/18	10/33	22.3	0.50
		4/19	15/54	30.4	0.67	5/24	13/45	31.2	0.66
0.30	0.50	7/22	17/46	29.9	0.67	7/28	15/39	35.0	0.36
		5/15	18/46	23.6	0.72	6/19	16/39	25.7	0.48
		8/24	24/63	34.7	0.73	7/24	21/53	36.6	0.56
0.40	0.60	7/18	22/46	30.2	0.56	11/28	20/41	33.8	0.55
		7/16	23/46	24.5	0.72	17/34	20/39	34.4	0.91
		11/25	32/66	36.0	0.73	12/29	27/54	38.1	0.64
0.50	0.70	11/21	26/45	29.0	0.67	11/23	23/39	31.0	0.50
		8/15	26/43	23.5	0.70	12/23	23/37	27.7	0.66
		13/24	36/61	34.0	0.73	14/27	32/53	36.1	0.65
0.60	0.80	6/11	26/38	25.4	0.47	18/27	24/35	28.5	0.82
		7/11	30/43	20.5	0.70	8/13	25/35	20.8	0.65
		12/19	37/53	29.5	0.69	15/26	32/45	35.9	0.48
0.70	0.90	6/9	22/28	17.8	0.54	11/16	20/25	20.1	0.55
		4/6	22/27	14.8	0.58	19/23	21/26	23.2	0.95
		11/15	29/36	21.2	0.70	13/18	26/32	22.7	0.67

*For each value of (p_0, p_1), designs are given for three sets of error probabilities (α, β). The first, second and third rows correspond to error probability limits (0.10, 0.10), (0.05, 0.20), and (0.05, 0.10) respectively. For each design, $EN(p_0)$ and $PET(p_0)$ denote the expected sample size and the probability of early termination when the true response probability is p_0.

Blow up: Simon (1989) Table

Table 1 Designs for $p_1 - p_0 = 0.20^a$

		Optimal Design			
		Reject Drug if Response Rate			
p_0	p_1	$\leq r_1/n_1$	$\leq r/n$	EN(p_0)	PET(p_0)
0.05	0.25	0/9	2/24	14.5	0.63
		0/9	2/17	12.0	0.63
		0/9	3/30	16.8	0.63
0.10	0.30	1/12	5/35	19.8	0.65
		1/10	5/29	15.0	0.74
		2/18	6/35	22.5	0.71
0.20	0.40	3/17	10/37	26.0	0.55
		3/13	12/43	20.6	0.75
		4/19	15/54	30.4	0.67

Phase II Example

- Initially enroll 17 patients.
  - 0-3 of the 17 have a clinical response then stop accrual and assume not an active agent
- If ≥ 4/17 respond, then accrual will continue to 37 patients

Phase II Example

- If 4-10 of the 37 respond this is insufficient activity to continue
- If ≥ 11/37 respond then the agent will be considered active
- Under this design if the null hypothesis were true (20% response probability) there is a 55% probability of early termination

Sample Size Differences

- If the null hypothesis (H_0) is true
- Using two-stage optimal design
  - On average 26 subjects enrolled
- Using a 1-sample test of proportions
  - 34 patients
  - If feasible
- Using a 2-sample randomized test of proportions
  - 86 patients per group

Phase II

- Newer methods are available
- Many cite Simon (thus, why we went through it)

Phase II: Historical Controls

- Want to double disease X survival from 15.7 months to 31 months.
- $\alpha = 0.05$, one tailed, $\beta = 0.20$
- Need 60 patients, about 30 in each of 2 arms; can accrue 1/month
- Need 36 months of follow-up
- Use historical controls

Phase II: Historical Controls

- Old data set from 35 patients treated at NCI with disease X, initially treated from 1980 to 1999
- Currently 3 of 35 patients alive
- Median survival time for historical patients is 15.7 months
- Almost like an observational study
- Use Dixon and Simon (1988) method for analysis

Phase II Summary

Study Design	*Advantages*	*Disadvantages*
1 arm	Small n	No control
1 arm 2-stage	Small n, stop early	No control, correct responder/non responder rules
Historical controls	Small n, some control	Accurate control ?
2(+) arm	Control	Larger n
8 arm	?	?

Phase III Survival Example

- Primary objective: determine if patients with metastatic melanoma who undergo Procedure A have a different overall survival compared with patients receiving standard of care (SOC)
- Trial is a two arm randomized phase III single institution trial

Number of Patients to Enroll?

- 1:1 ratio between the two arms
- 80% power to detect a difference between 8 month median survival and 16 month median survival
- Two-tailed α = 0.05
- 24 months of follow-up after the last patient has been enrolled
- 36 months of accrual

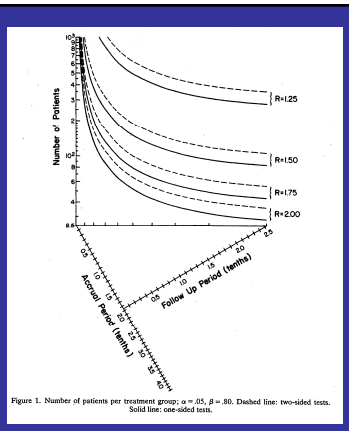
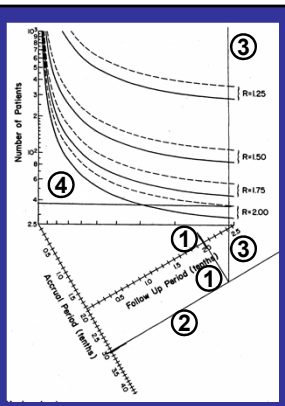
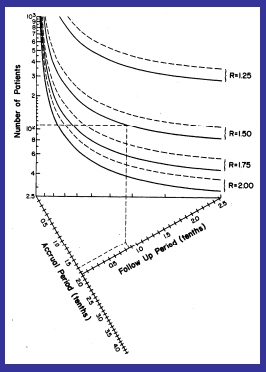


Figure 1. Number of patients per treatment group; α = .05, β = .80. Dashed line: two-sided tests. Solid line: one-sided tests.



Phase III Survival

- Look at nomograms (Schoenfeld and Richter). Can use formulas
- Need 38/arm, so let's try to recruit 42/arm – total of 84 patients
- Anticipate approximately 30 patients/year entering the trial



Non-Survival Simple Sample Size

- Start with 1-arm or 1-sample study
- Move to 2-arm study
- Study with 3+ arms cheat trick
  - Calculate PER ARM sample size for 2-arm study
  - Use that PER ARM
  - Does not always work; typically ok

1-Sample N Example

- Study effect of new sleep aid
- 1 sample test
- Baseline to sleep time after taking the medication for one week
- Two-sided test, α = 0.05, power = 90%
- Difference = 1 (4 hours of sleep to 5)
- Standard deviation = 2 hr

Sleep Aid Example

- 1 sample test
- 2-sided test, α = 0.05, 1-β = 90%
- σ = 2hr (standard deviation)
- δ = 1 hr (difference of interest)

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2} = \frac{(1.960 + 1.282)^2 2^2}{1^2} = 42.04 \approx 43$$

Sample Size: Change Effect or Difference

- Change difference of interest from 1hr to 2 hr
- n goes from 43 to 11

$$n = \frac{(1.960 + 1.282)^2 2^2}{2^2} = 10.51 \approx 11$$

Sample Size: Iteration and the Use of *t*

- Found n = 11 using Z
- Use t_{10} instead of Z
  - t_{n-1} for a simple 1 sample
- Recalculate, find n = 13
- Use t_{12}
- Recalculate sample size, find n = 13
  - Done
- Sometimes iterate several times

Sample Size: Change Power

- Change power from 90% to 80%
- n goes from 11 to 8
- (Small sample: start thinking about using the t distribution)

$$n = \frac{(1.960 + 0.841)^2 2^2}{2^2} = 7.85 \approx 8$$

Sample Size: Change Standard Deviation

- Change the standard deviation from 2 to 3
- n goes from 8 to 18

$$n = \frac{(1.960 + 0.841)^2 3^2}{2^2} = 17.65 \approx 18$$

Sleep Aid Example: 2 Arms Investigational, Control

- Original design (2-sided test, α = 0.05, 1-β = 90%, σ = 2hr, δ = 1 hr)
- Two sample randomized parallel design
- Needed 43 in the one-sample design
- In 2-sample need twice that, in each group!
- 4 times as many people are needed in this design

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2} = \frac{2(1.960 + 1.282)^2 2^2}{1^2} = 84.1 \approx 85 \rightarrow 170 \text{ total!}$$

Sleep Aid Example: 2 Arms Investigational, Control

- Original design (2-sided test, α = 0.05, 1-β = 90%, σ = 2hr, δ = 1 hr)
- Two sample randomized parallel design
- Needed 43 in the one-sample design
- In 2-sample need twice that, in each group!
- 4 times as many people are needed in this design

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2} = \frac{2(1.960 + 1.282)^2 2^2}{1^2} = 84.1 \approx 85 \rightarrow 170 \text{ total!}$$

Aside: 5 Arm Study

- Sample size per arm = 85
- 85*5 = 425 total
  - Similar 5 arm study
  - Without considering multiple comparisons

Sample Size: Change Effect or Difference

- Change difference of interest from 1hr to 2 hr
- n goes from 170 to 44

$$n = \frac{2(1.960 + 1.282)^2 2^2}{2^2} = 21.02 \approx 22 \rightarrow 44 \text{ total}$$

Sample Size: Change Power

- Change power from 90% to 80%
- n goes from 44 to 32

$$n = \frac{2(1.960 + 0.841)^2 2^2}{2^2} = 15.69 \approx 16 \rightarrow 32 \text{ total}$$

Sample Size: Change Standard Deviation

- Change the standard deviation from 2 to 3
- n goes from 32 to 72

$$n = \frac{2(1.960 + 0.841)^2 3^2}{2^2} = 35.31 \approx 36 \rightarrow 72 \text{ total}$$

Conclusion

- Changes in the difference of interest have HUGE impacts on sample size
  - 20 point difference → 25 patients/group
  - 10 point difference → 100 patients/group
  - 5 point difference → 400 patients/group
- Changes in difference to be detected, α, β, σ, number of samples, if it is a 1- or 2-sided test can all have a large impact on your sample size calculation

2-Arm Study's TOTAL Sample Size = $2N = \frac{4(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2}$

Other Designs?

Sample Size: Matched Pair Designs

- Similar to 1-sample formula
- Means (paired t-test)
  - Mean difference from paired data
  - Variance of differences
- Proportions
  - Based on discordant pairs

Examples in the Text

- Several with paired designs
- Two and one sample means
- Proportions
- How to take pilot data and design the next study

Cohen's Effect Sizes

- Large (.8), medium (.5), small (.2)
- Popular especially in social sciences
- Do NOT use unless no choice
  - Need to think
- 'Medium' yields same sample size regardless of what you are measuring

Outline

- ✓ Power
- ✓ Basic sample size information
- ✓ Examples (see text for more)
- ➢ Changes to the basic formula/ Observational studies
- Multiple comparisons
- Rejected sample size statements
- Conclusion and Resources

Unequal #s in Each Group

- Ratio of cases to controls
- Use if want λ patients randomized to the treatment arm for every patient randomized to the placebo arm
- Take no more than 4-5 controls/case

$$n_2 = \lambda n_1 \rightarrow \lambda \text{ controls for every case}$$

$$n_1 = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2(\sigma_1^2 + \sigma_2^2/\lambda)}{\delta^2}$$

K:1 Sample Size Shortcut

- Use equal variance sample size formula: TOTAL sample size increases by a factor of
  $(k+1)^2/4k$
- Ex: Total sample size for two equal groups = 26; want 2:1 ratio
- $26*(2+1)^2/(4*2) = 26*9/8 = 29.25 \approx 30$
- 20 in one group and 10 in the other

Unequal #s in Each Group: Fixed # of Cases

- Only so many new devices
- Sample size calculation says n=13 per arm needed
- Only have 11 devices!
- Want the same precision
- n_0 = 11 device recipients
- kn_0 = # of controls

How many controls?

$$k = \frac{n}{2n_0 - n}$$

- k = 13 / (2*11 – 13) = 13 / 9 = 1.44
- kn_0 = 1.44*11 ≈ 16 controls (and 11 cases) = 27 total (controls + cases)
  - Same precision as 13 controls and 13 cases (26 total)

of Events is Important

- Cohort of exposed and unexposed people
- Relative Risk = R
- Prevalence in the unexposed population = π_1

Formulas and Example

$$R = \frac{\text{Risk of event in exposed group}}{\text{Risk of event in unexposed group}}$$

$$n_1 = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{2(\sqrt{R} - 1)^2} = \#\text{of events in unexposed group}$$

$n_2 = Rn_1 = \#$events in exposed group

n_1 and n_2 are the number of events in the two groups required to detect a relative risk of R with power 1-β

$N = n_1 / \pi_1 =$ # subjects per group

of Covariates and # of Subjects

- At least 10 subjects for every variable investigated
  - In logistic regression
  - No general theoretical justification
  - This is stability, not power
  - Peduzzi et al., (1985) unpredictable biased regression coefficients and variance estimates
- Principal component analysis (PCA) (Thorndike 1978 p 184): $N \geq 10m+50$ or even $N \geq m^2 + 50$

Balanced Designs: Easier to Find Power / Sample Size

- Equal numbers in two groups is the easiest to handle
- If you have more than two groups, still, equal sample sizes easiest
- Complicated design = simulations
  - Done by the statistician

Outline

✓Power
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✓Changes to the basic formula
➢Multiple comparisons
- Rejected sample size statements
- Conclusion and Resources

Multiple Comparisons

- If you have 4 groups
  - All 2 way comparisons of means
  - 6 different tests
- Bonferroni: divide α by # of tests
  - 0.025/6 ≈ 0.0042
  - Common method; long literature
- High-throughput laboratory tests

DNA Microarrays/Proteomics

- Same formula (Simon et al. 2003)
  - $\alpha = 0.001$ and $\beta = 0.05$
  - Possibly stricter
- Many other methods

Outline

✓Power
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No, not from your grant application…..

- Statistics Guide for Research Grant Applicants
- St. George's Hospital Medical School Department of Public Health Sciences
- http://www-users.york.ac.uk/~mb55/guide/guide14.pdf
- EXCELLENT resource

Me, too! No, Please Justify N

- "A previous study in this area recruited 150 subjects and found highly significant results (p=0.014), and therefore a similar sample size should be sufficient here."
  - Previous studies may have been 'lucky' to find significant results, due to random sampling variation

No Prior Information

- "Sample sizes are not provided because there is no prior information on which to base them."
  - Find previously published information
  - Conduct small pre-study
  - If a very preliminary pilot study, sample size calculations not usually necessary

Variance?

- No prior information on standard deviations
  - Give the size of difference that may be detected in terms of number of standard deviations

Number of Available Patients

- "The clinic sees around 50 patients a year, of whom 10% may refuse to take part in the study. Therefore over the 2 years of the study, the sample size will be 90 patients. "
  - Although most studies need to balance feasibility with study power, the sample size should not be decided on the number of available patients alone.
  - If you know # of patients is an issue, can phrase in terms of power

Outline

✓Power
✓Basic Sample Size Information
✓Examples (see text for more)
✓Changes to the basic formula
✓Multiple comparisons
✓Rejected sample size statements
➢Conclusion and Resources

Conclusions: What Impacts Sample Size?

- Difference of interest
  - 20 point difference → 25 patients/group
  - 5 point difference → 400 patients/group
- σ, α, β
- Number of arms or samples
- 1- or 2-sided test

Total Sample Size 2-Armed/Group/Sample Test

$$2N = \frac{4(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2}$$

No Estimate of the Variance?

- Make a sample size or power table
- Make a graph
- Use a wide variety of possible standard deviations
- Protect with high sample size if possible

Top 10 Statistics Questions

10. Exact mechanism to randomize patients
9. Why stratify? (EMA re: dynamic allocation
8. Blinded/masked personnel
   - ➢ Endpoint assessment

Top 10 Statistics Questions

7. Each hypothesis
   - Specific analyses
   - Specific sample size
6. How / if adjusting for multiple comparisons
5. Effect modification

Top 10 Statistics Questions

4. Interim analyses (if yes)
   - What, when, error spending model / stopping rules
   - Accounted for in the sample size ?
3. Expected drop out (%)
2. How to handle drop outs and missing data in the analyses?

Top 10 Statistics Questions

1. Repeated measures / longitudinal data
   - Use a linear mixed model instead of repeated measures ANOVA
     - Many reasons to NOT use repeated measures ANOVA; few reasons to use
   - Similarly generalized estimating equations (GEE) if appropriate

Analysis Follows Design

Questions → Hypotheses →
Experimental Design → Samples →
Data → Analyses →Conclusions

- Take all of your design information to a statistician early and often
  - Guidance
  - Assumptions

Another Take? Paul Wakim

- www.youtube.com/watch?v=Zl8tGWNcKLI
- Lecture for IPPCR course in Brazil September 2014
- More focused on later phase studies
- Excellent examples

Questions?

Resources: General Books

- Hulley et al (2001) *Designing Clinical Research, 2nd ed.* LWW
- Rosenthal (2006) *Struck by Lightning: The curious world of probabilities*
- Bland (2000) *An Introduction to Medical Statistics, 3rd. ed.* Oxford University Press
- Armitage, Berry and Matthews (2002) *Statistical Methods in Medical Research, 4th ed.* Blackwell, Oxford

Resources: General/Text Books

- Altman (1991) *Practical Statistics for Medical Research.* Chapman and Hall
- Fisher and Van Belle (1996, 2004) Wiley
- Simon et al. (2003) *Design and Analysis of DNA Microarray Investigations.* Springer Verlag
- Rosner *Fundamentals of Biostatistics*. Choose an edition. Has a study guide, too.

Sample Size Specific Tables

- Continuous data: Machin *et al.* (1998) *Statistical Tables for the Design of Clinical Studies, Second Edition* Blackwell, Oxford
- Categorical data: Lemeshow *et al.* (1996) *Adequacy of sample size in health studies.* Wiley
- Sequential trials: Whitehead, J. (1997) *The Design and Analysis of Sequential Clinical Trials, revised 2nd. ed.* Wiley
- Equivalence trials: Pocock SJ. (1983) *Clinical Trials: A Practical Approach.* Wiley

Resources: Articles

- Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*. 10:1-10, 1989.
- Thall, Simon, Ellenberg. A two-stage design for choosing among several experimental treatments and a control in clinical trials. *Biometrics.* 45(2):537-547, 1989.

Resources: Articles

- Schoenfeld, Richter. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics.* 38(1):163-170, 1982.
- Bland JM and Altman DG. One and two sided tests of significance. *British Medical Journal* 309: 248, 1994.
- Pepe, Longton, Anderson, Schummer. Selecting differentially expressed genes from microarry experiments. *Biometrics.* 59(1):133-142, 2003.

Regulatory Guidances

- ICH E9 Statistical principles
- ICH E10: Choice of control group and related issues
- ICH E4: Dose response
- ICH E8: General considerations
- US FDA guidance and draft guidance on drug interaction study designs (and analyses), Bayesian methods, etc.
  - http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm

Resources: URLs

- Sample size calculations simplified
  - http://www.jerrydallal.com/LHSP/SIZE.HTM
- Stat guide: research grant applicants, St. George's Hospital Medical School
  (http://www-users.york.ac.uk/~mb55/guide/guide.htm)
  - http://tinyurl.com/7qpzp2j
- Software: nQuery, EpiTable, SeqTrial, PS
  (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize)
  - http://tinyurl.com/zoysm
- Earlier lectures

Various Sites by Steve Simon

- www.pmean.com/category/HumanSideStatistics.html
- www.pmean.com/category/RandomizationInResearch.html
- www.pmean.com/category/SampleSizeJustification.html
- http://www.cs.uiowa.edu/~rlenth/Power/