

# Sample Size and Power

Chapter 22, 3<sup>rd</sup> Edition

Chapter 15, 2<sup>nd</sup> 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

# 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 ( $\delta$ )
- Variation in the outcome ( $\sigma^2$ )
- Significance level ( $\alpha$ )
  - 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

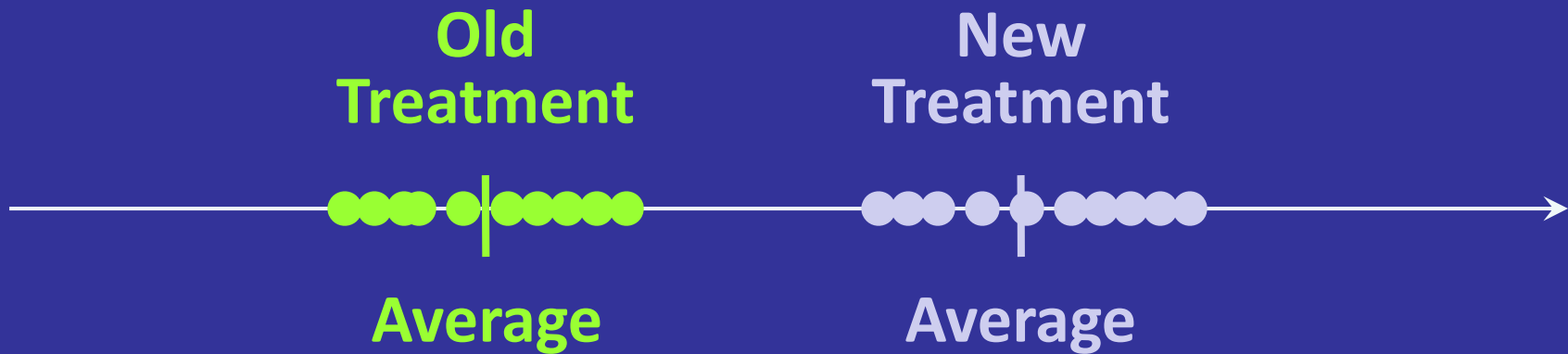
# Answer

Without *variability*, there is no need for  
Statistics

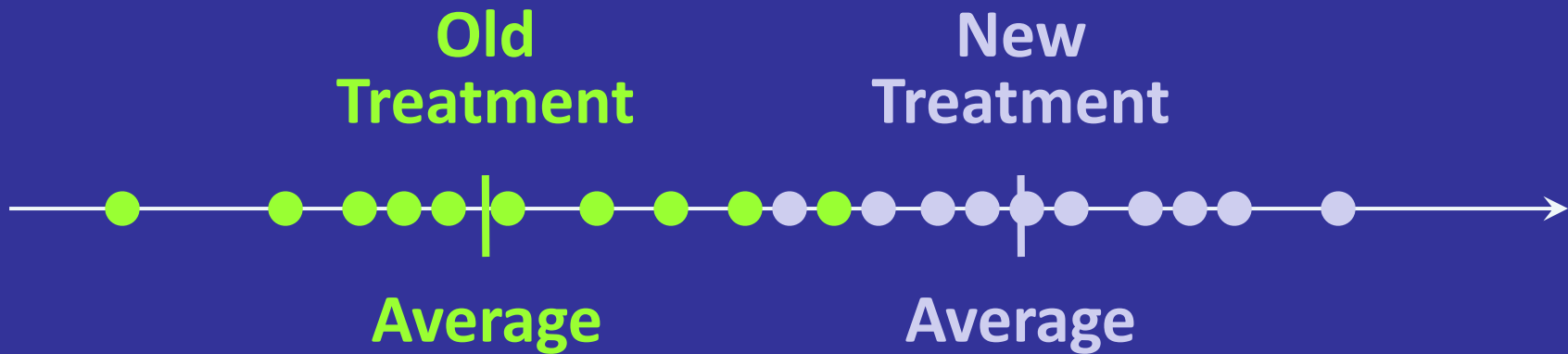
# Variability



# Variability



# Variability



# Variability



# 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 =  $1 - \beta = P(\text{reject } H_0 \mid H_1 \text{ true})$ 
  - “Probability of rejecting the null hypothesis if the alternative hypothesis is true.”
- More subjects  $\rightarrow$  higher power



# Power is Affected by.....

- **Variation in the outcome ( $\sigma^2$ )**
  - $\downarrow \sigma^2 \rightarrow \text{power} \uparrow$
- **Significance level ( $\alpha$ )**
  - $\uparrow \alpha \rightarrow \text{power} \uparrow$
- **Difference (effect) to be detected ( $\delta$ )**
  - $\uparrow \delta \rightarrow \text{power} \uparrow$
- **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,  $\delta=2$ ,  $\sigma = 2$ ,  $\alpha = 0.05$ , 2-sided test
- **Variance/Standard deviation**
  - $\sigma: 2 \rightarrow 1$  Power: 81%  $\rightarrow$  99.99%
  - $\sigma: 2 \rightarrow 3$  Power: 81%  $\rightarrow$  47%
- **Significance level ( $\alpha$ )**
  - $\alpha : 0.05 \rightarrow 0.01$  Power: 81%  $\rightarrow$  69%
  - $\alpha : 0.05 \rightarrow 0.10$  Power: 81%  $\rightarrow$  94%

# Power Changes

- $2n = 32$ , 2 sample test, 81% power,  $\delta=2$ ,  $\sigma = 2$ ,  $\alpha = 0.05$ , 2-sided test
- **Difference to be detected ( $\delta$ )**
  - $\delta : 2 \rightarrow 1$  Power: 81%  $\rightarrow$  29%
  - $\delta : 2 \rightarrow 3$  Power: 81%  $\rightarrow$  99%
- **Sample size (n)**
  - n: 32  $\rightarrow$  64 Power: 81%  $\rightarrow$  98%
  - n: 32  $\rightarrow$  28 Power: 81%  $\rightarrow$  75%
- **Two-tailed vs. One-tailed tests**
  - Power: 81%  $\rightarrow$  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,  $\alpha$ ,  $\beta$ ,  $\sigma$ , 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**

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

# 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)**
  - Changes to the basic formula
  - Multiple comparisons
  - Rejected sample size statements
  - Conclusion and Resources

# 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



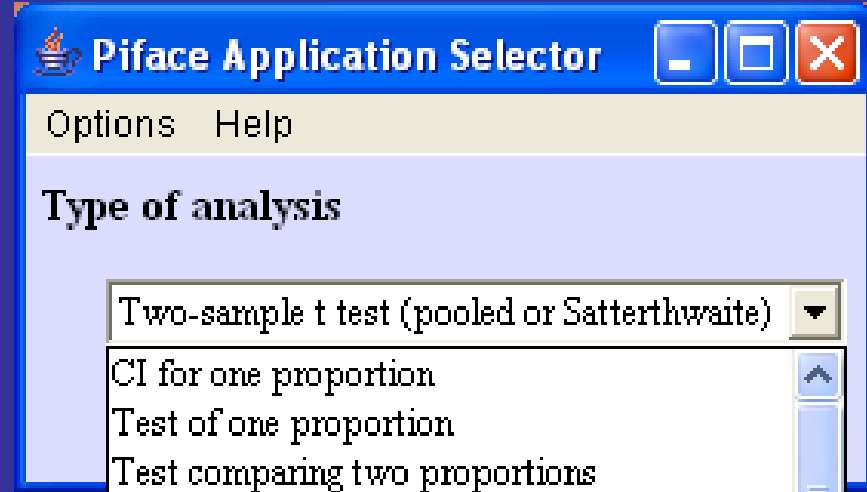
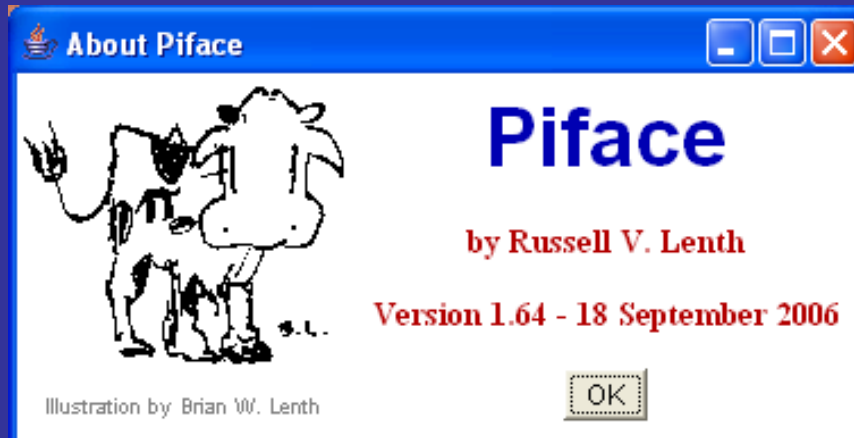
# Live Statistical Consult!

- 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

Two-sample t test (general case)

Options Help

Two-tailed Alpha

Equivalence

signal = 1

sigma2 = 1

Equal sigmas

Degrees of freedom = 48

True difference of means = .5

n1 = 25

n2 = 25

Allocation

Power = .4101

Solve for

Two-sample t test (general case)

Options Help

Two-tailed Alpha

Equivalence

signal = 1

sigma2

Value  OK

Value

Min

Max

Min!

Max!

Digits

Degrees of freedom = 48

True difference of means = .5

n2 = 25

Allocation

Power = .4101

Solve for

# 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  $n = \text{XXXX}$

# 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

**Two-sample t test (general case)**

Options Help

signal = 2

sigma2

Value 2 OK

Equal sigmas

n1 = 85

n2 = 85

Allocation Equal

Two-tailed Alpha .05

Equivalence

Degrees of freedom = 168

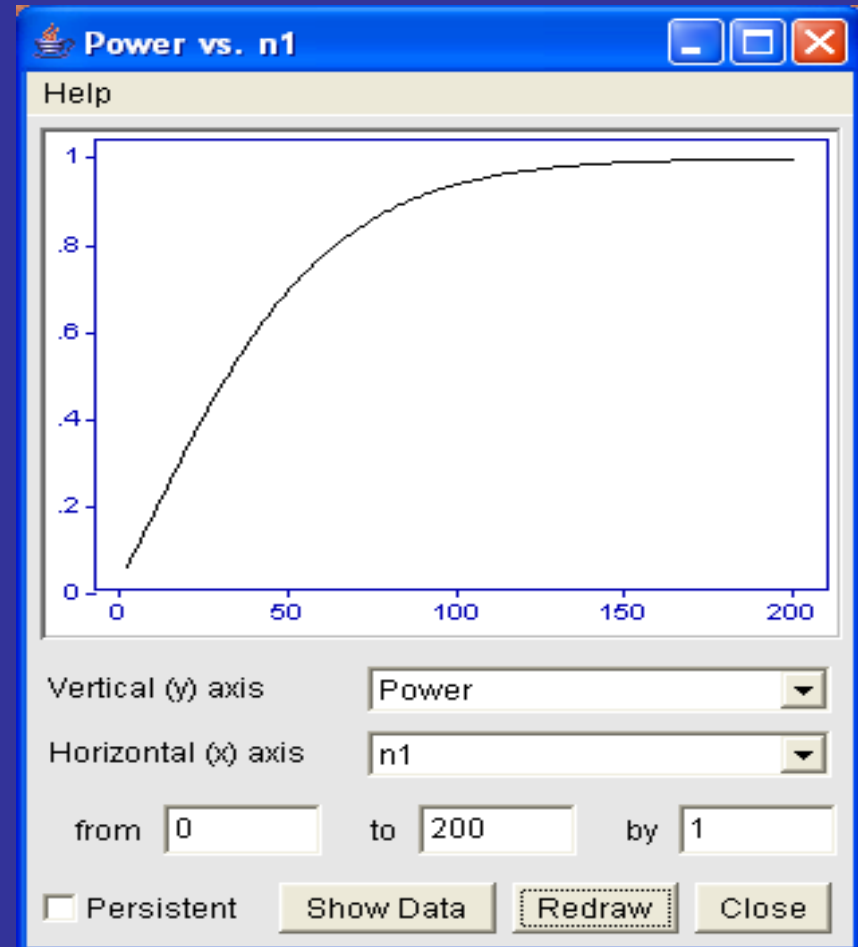
True difference of means

Value 1 OK

Power

Value .8999 OK

Solve for Sample size



# 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**

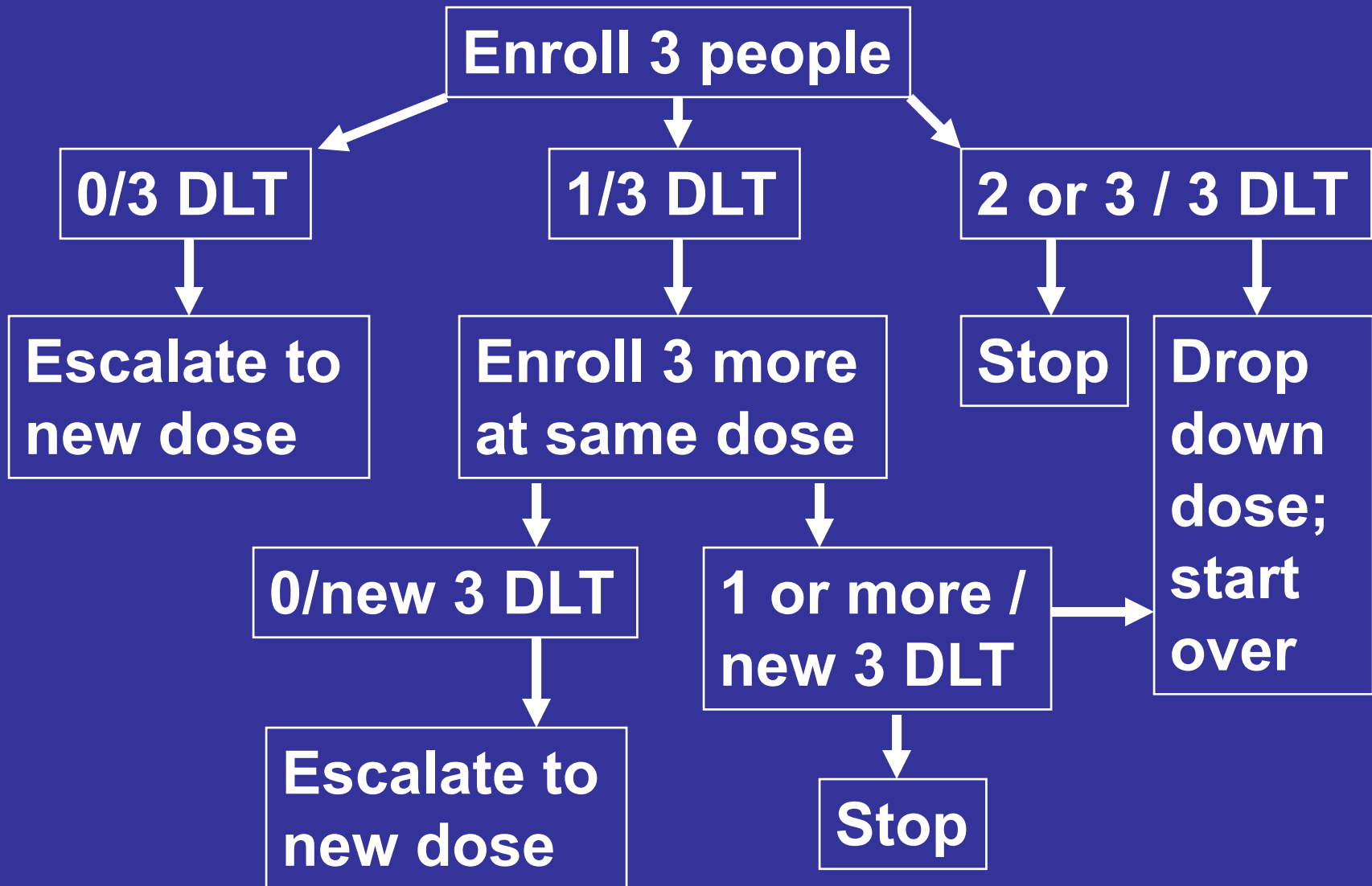
# Phase I (Old Way)

- **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)

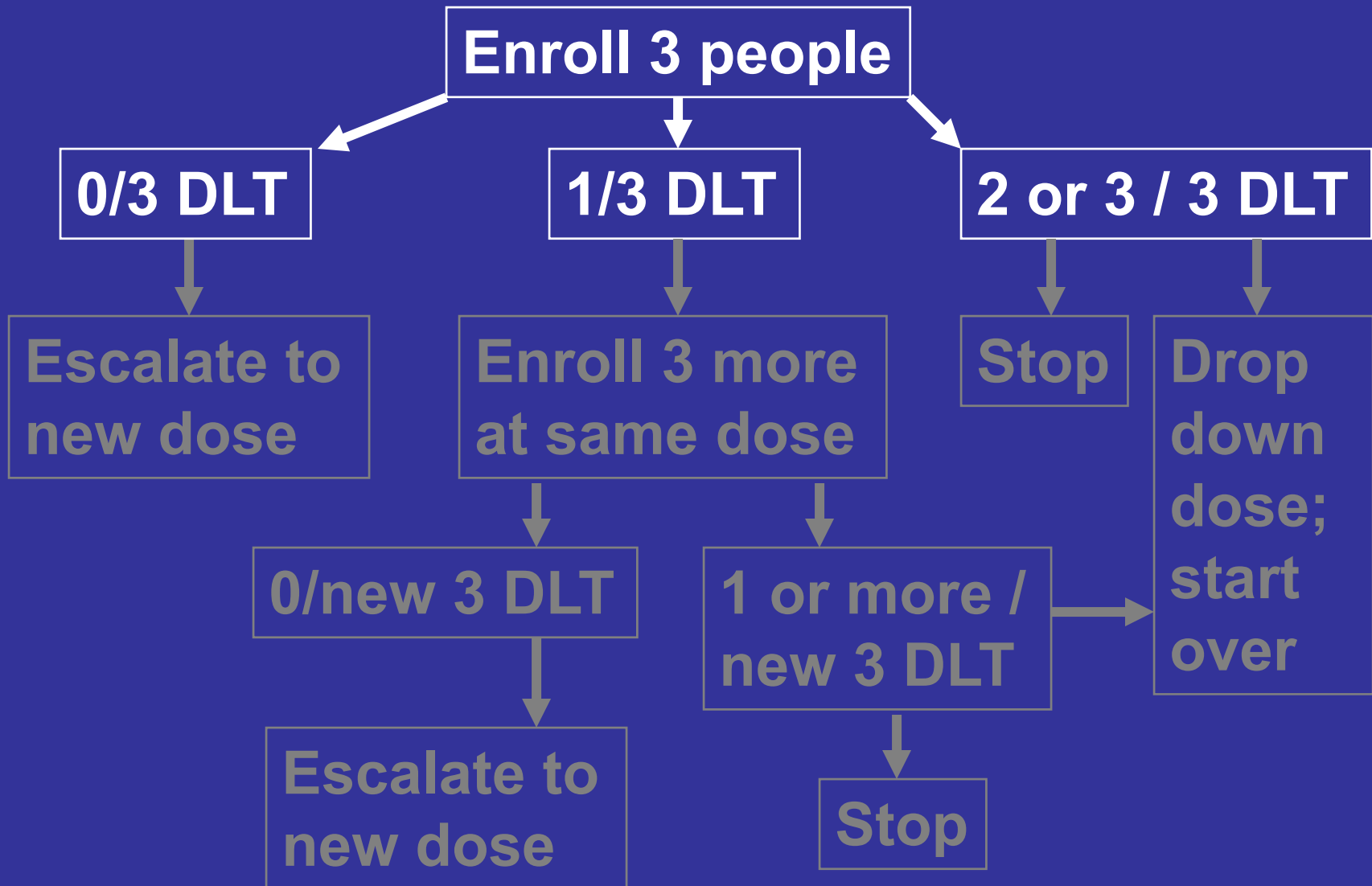
# Phase I (cont.)

- **Maximum Tolerated Dose (MTD)**
  - Dose level immediately below the level at which  $\geq 2$  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

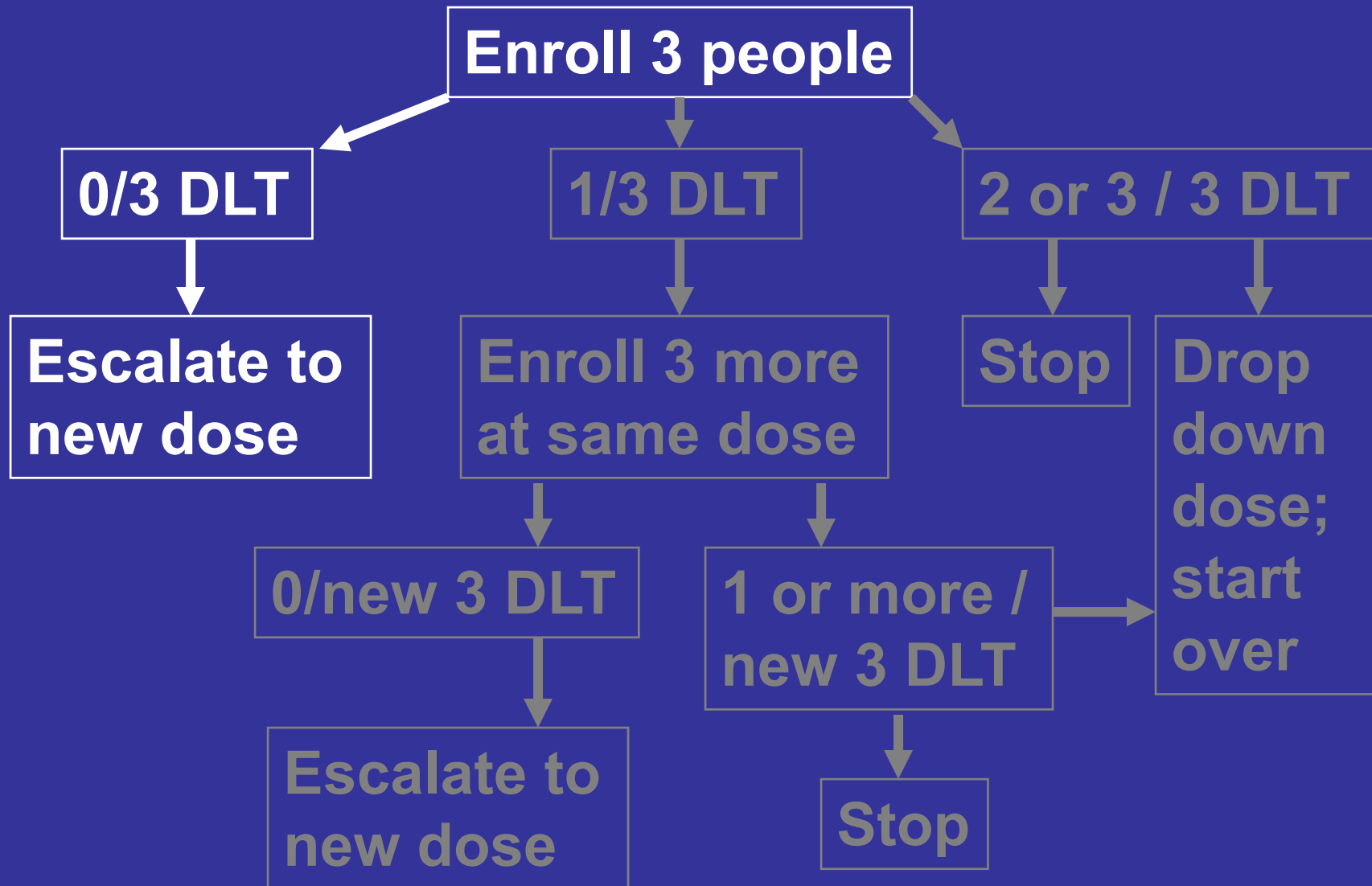
# Phase I



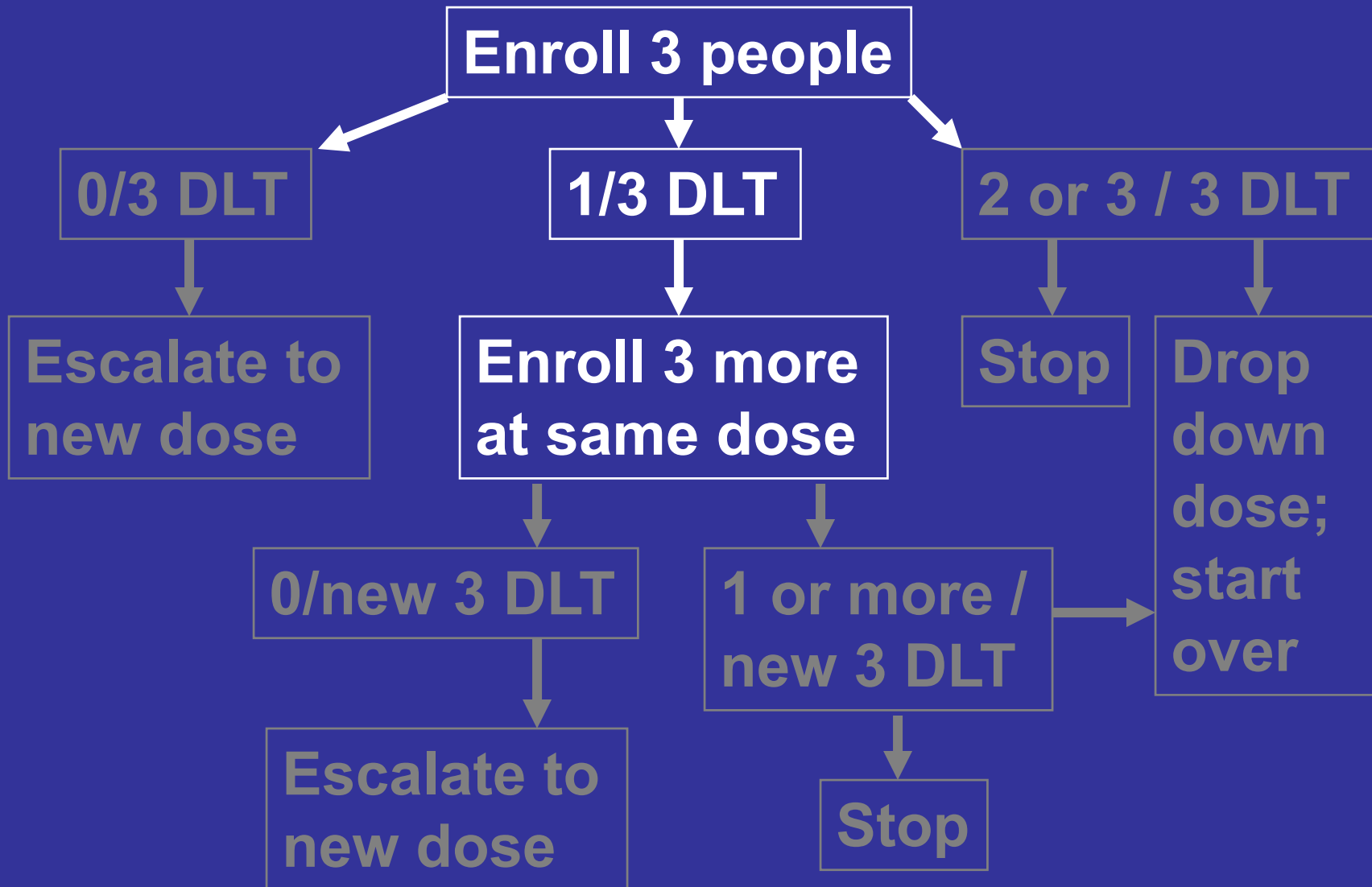
# Phase I



# Phase I

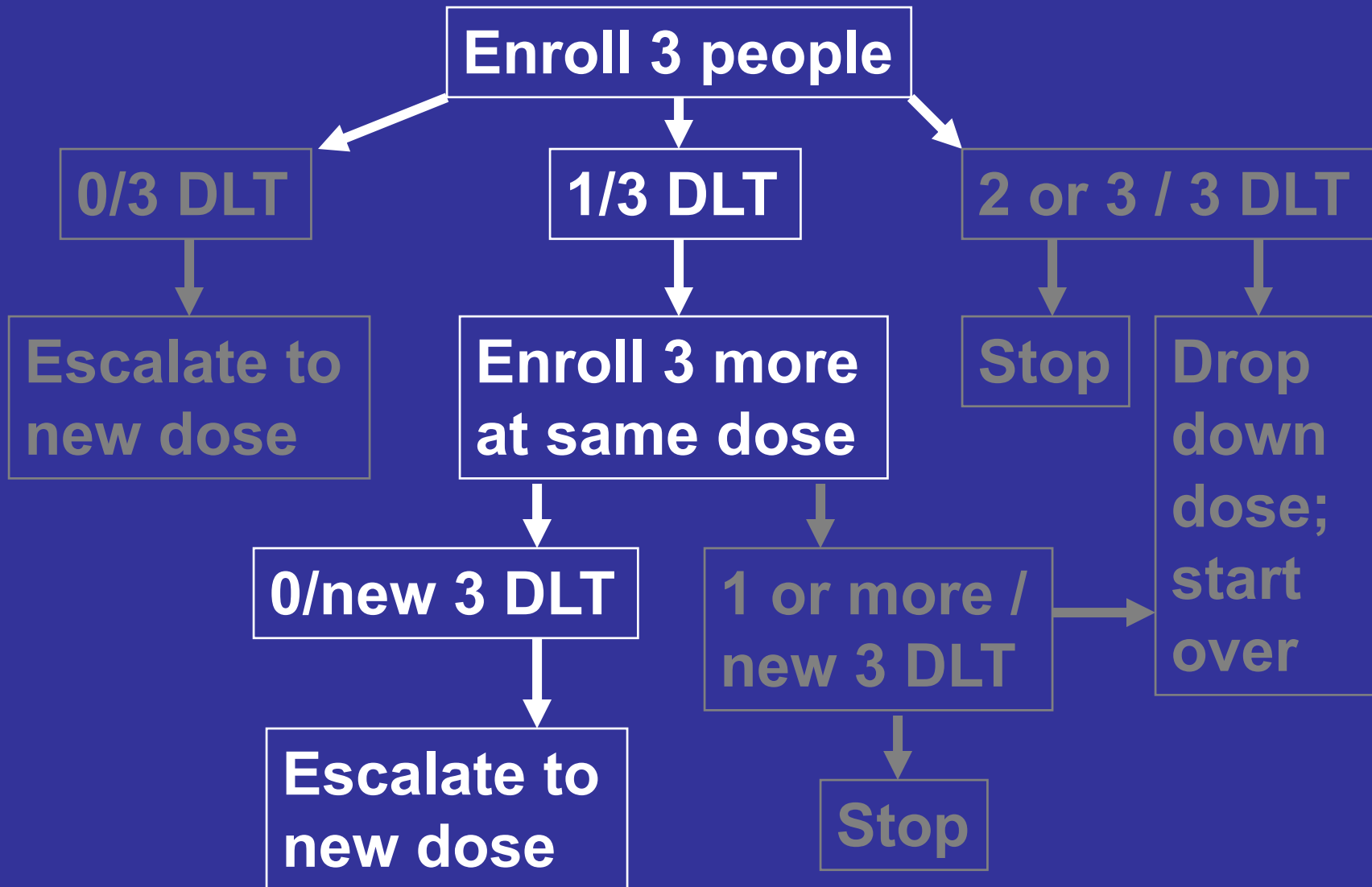


# Phase I

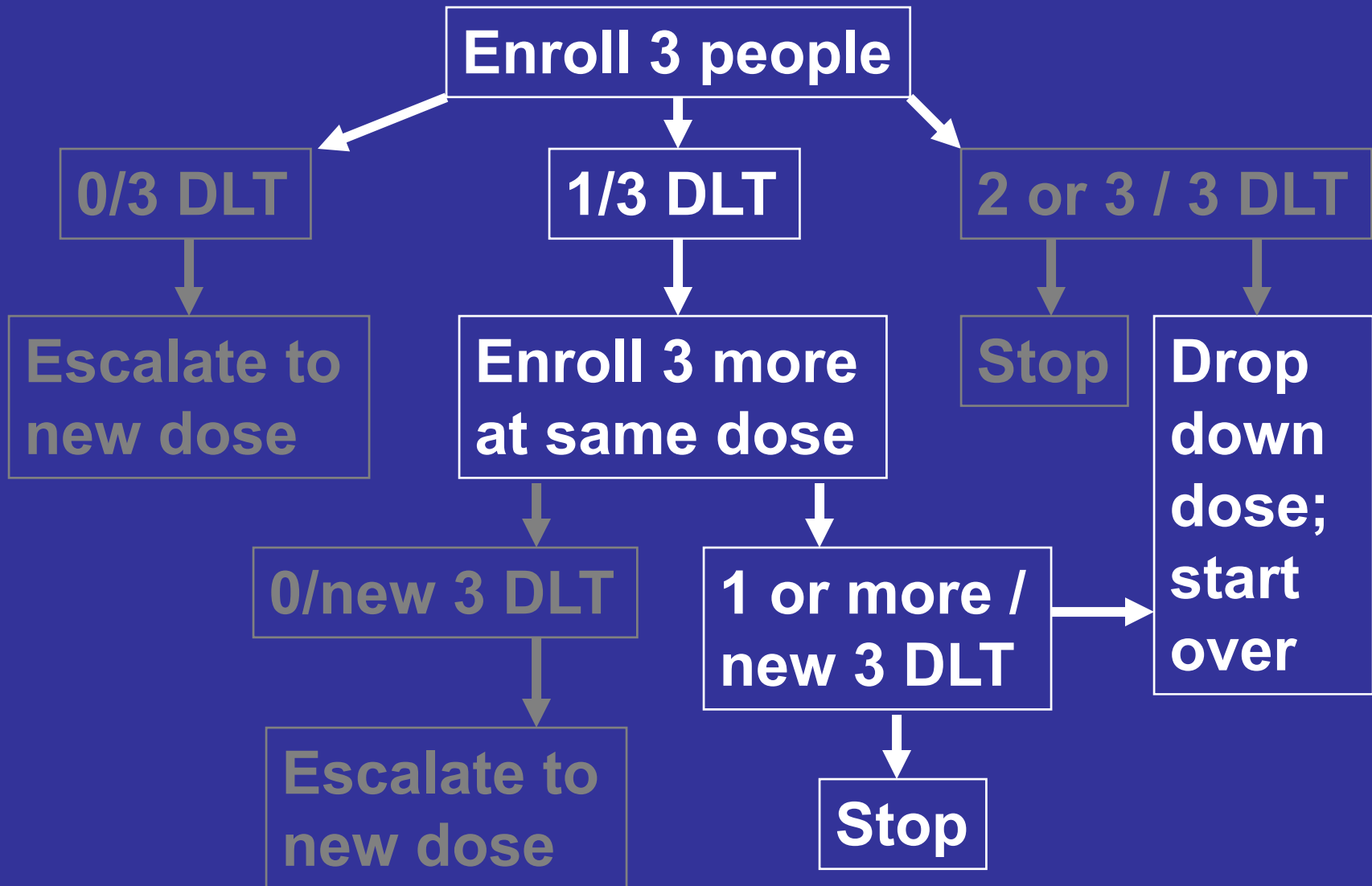




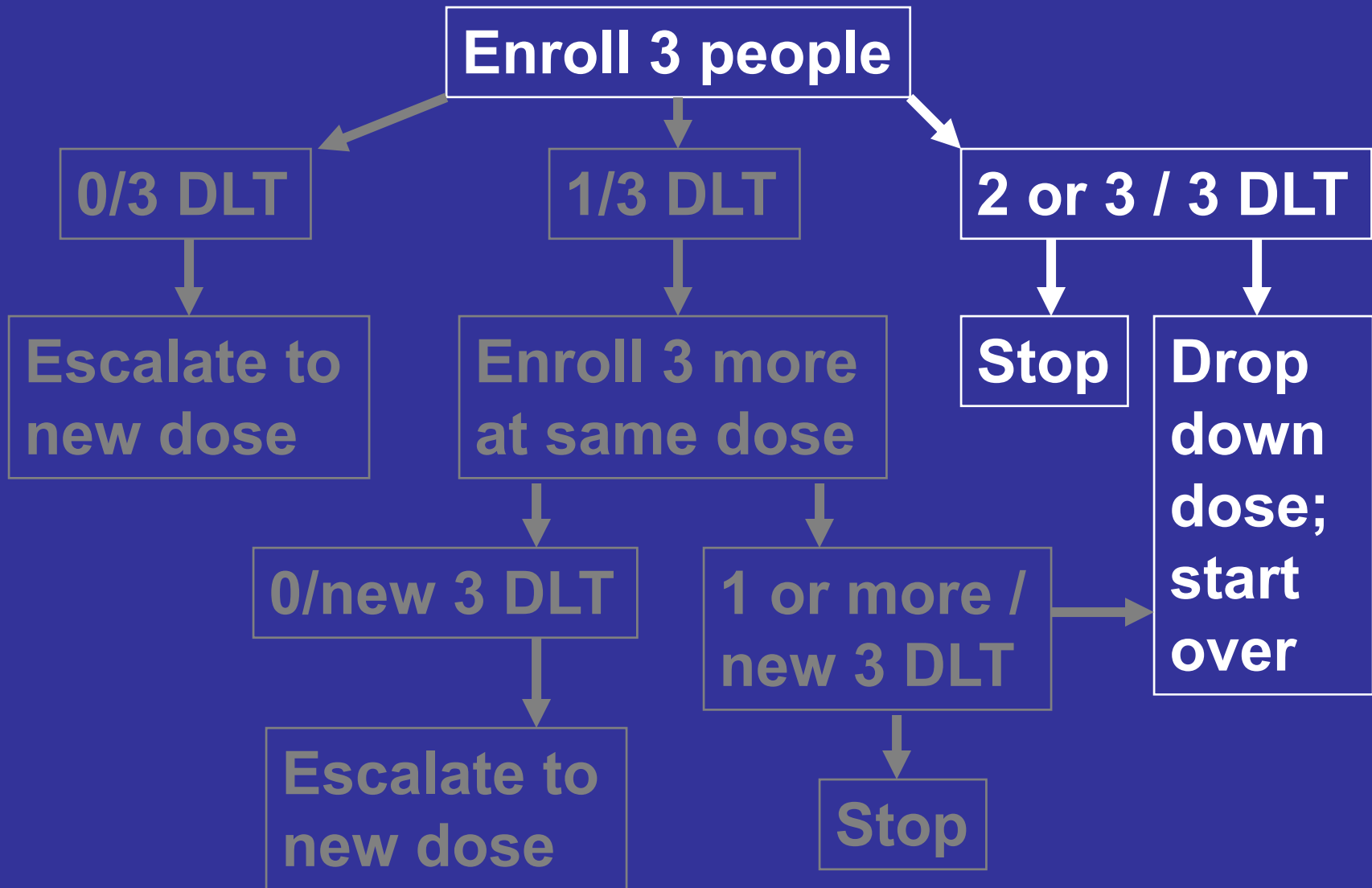
# Phase I



# Phase I



# Phase I



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

# Phase I Note

- \*Implicitly targets a dose with Pr (Toxicity)  $\leq 0.17$ ; if at  $1/3+1/3$  decide *current* level is MTD then the Pr (Toxicity)  $\leq 0.33$
- 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 ( $p_0=0.20$ )
- **Seek to rule out  $p_0$  in favor of  $p_1$ ; shows “useful” activity**
  - E.g. 40% are stable ( $p_1=0.40$ )

## 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% ( $H_1: p=0.40$ )
- $\alpha = 0.10$ ,  $\beta = 0.10$

# Two-Stage Optimal Design

- Let  $\alpha = 0.1$  (10% probability of accepting a poor agent)
- Let  $\beta = 0.1$  (10% probability of rejecting a good agent)
- Charts in Simon (1989) paper with different  $p_1 - p_0$  amounts and varying  $\alpha$  and  $\beta$  values

# Table from Simon (1989)

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

$p_0$	$p_1$	Optimal Design				Minimax Design			
		Reject Drug if Response Rate		EN( $p_0$ )	PET( $p_0$ )	Reject Drug if Response Rate		EN( $p_0$ )	PET( $p_0$ )
		$\leq r_1/n_1$	$\leq r/n$			$\leq r_1/n_1$	$\leq r/n$		
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

<sup>a</sup>For each value of  $(p_0, p_1)$ , designs are given for three sets of error probabilities  $(\alpha, \beta)$ . 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  $p_1 - p_0 = 0.20^a$

$p_0$	$p_1$	Optimal Design			
		Reject Drug if Response Rate		EN( $p_0$ )	PET( $p_0$ )
		$\leq r_1/n_1$	$\leq r/n$		
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  $\geq 4/17$  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  $\geq 11/37$  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

<i>Study Design</i>	<i>Advantages</i>	<i>Disadvantages</i>
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  $\alpha = 0.05$
- 24 months of follow-up after the last patient has been enrolled
- 36 months of accrual

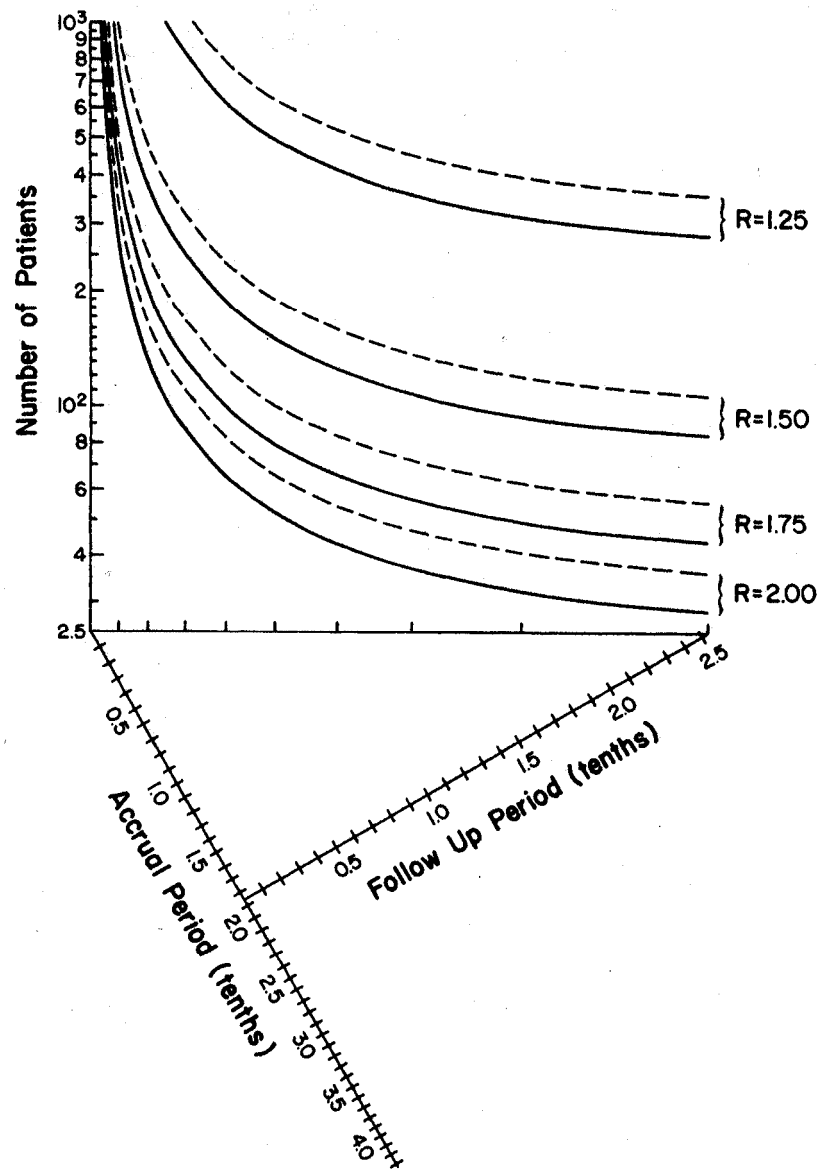
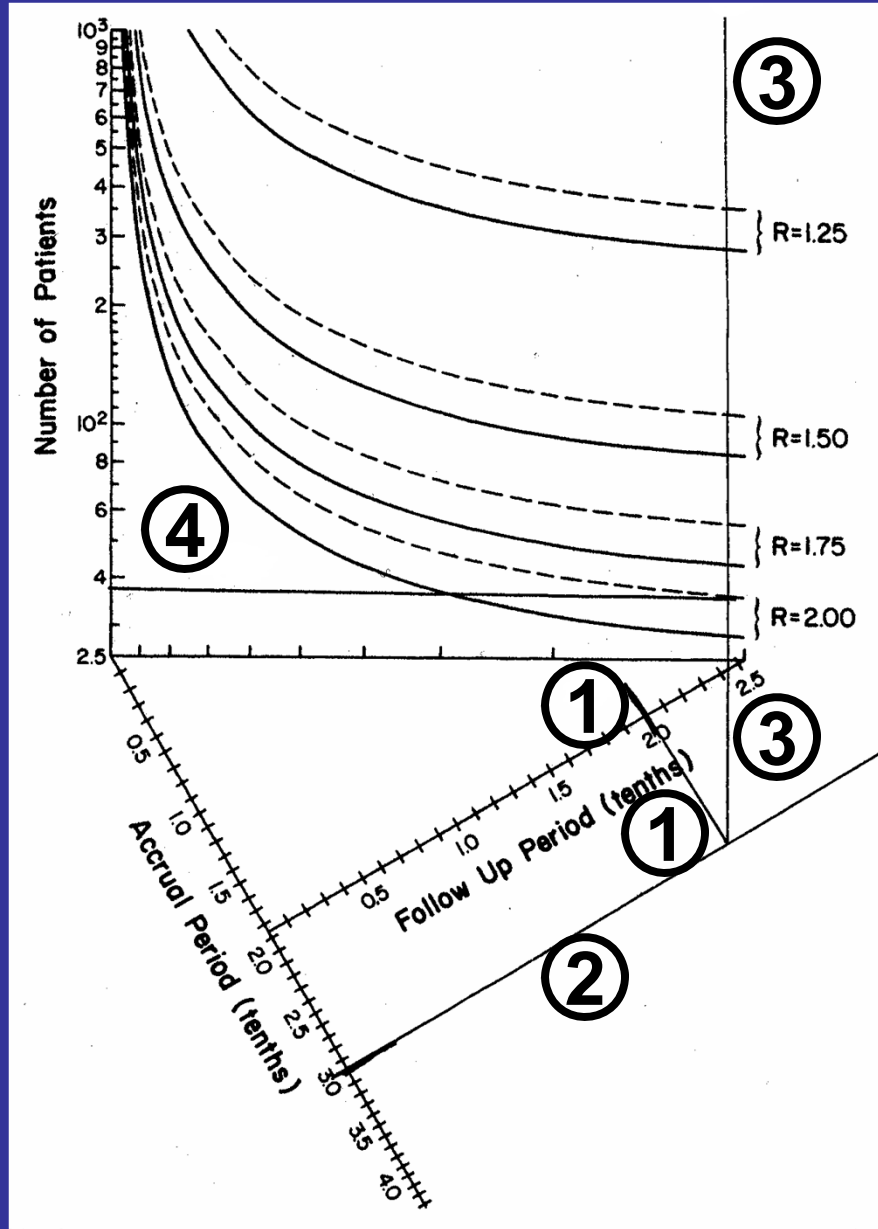


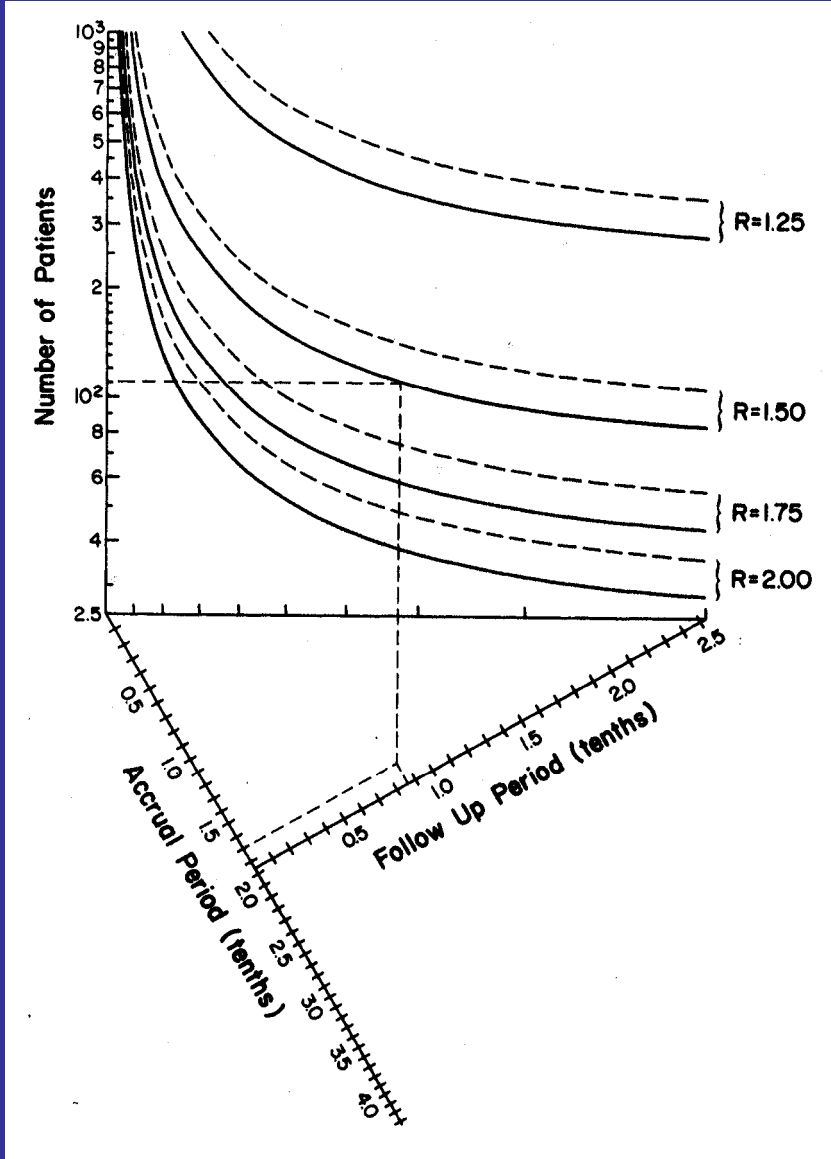
Figure 1. Number of patients per treatment group;  $\alpha = .05$ ,  $\beta = .80$ . Dashed line: two-sided tests. Solid line: one-sided tests.





# 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,  $\alpha = 0.05$ , power = 90%
- Difference = 1 (4 hours of sleep to 5)
- Standard deviation = 2 hr

# Sleep Aid Example

- 1 sample test
- 2-sided test,  $\alpha = 0.05$ ,  $1-\beta = 90\%$
- $\sigma = 2\text{hr}$  (standard deviation)
- $\delta = 1\text{ hr}$  (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,  $\alpha = 0.05$ ,  $1-\beta = 90\%$ ,  $\sigma = 2\text{hr}$ ,  $\delta = 1\text{ hr}$ )
- 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

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


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# 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,  $\alpha$ ,  $\beta$ ,  $\sigma$ , 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**

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



**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  $\lambda$  patients randomized to the treatment arm for every patient randomized to the placebo arm
- Take no more than 4-5 controls/case

$n_2 = \lambda n_1 \rightarrow \lambda$  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
- $26 \cdot (2+1)^2 / (4 \cdot 2) = 26 \cdot 9 / 8 = 29.25 \approx 30$
- 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?

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

- $k = 13 / (2*11 - 13) = 13 / 9 = 1.44$
- $kn_0 = 1.44*11 \approx 16$  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 =  $\pi_1$

# Formulas and Example

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

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

$$n_2 = Rn_1 = \text{\#events in exposed group}$$

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

$$N = n_1 / \pi_1 = \text{\# subjects per group}$$

# # 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
- ✓ Basic Sample Size Information
- ✓ Examples (see text for more)
- ✓ 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  $\alpha$  by # of tests
  - $0.025/6 \approx 0.0042$
  - 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
- ✓ Basic Sample Size Information
- ✓ Examples (see text for more)
- ✓ Changes to the basic formula
- ✓ Multiple comparisons
- **Rejected sample size statements**
- **Conclusion and Resources**

# **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
- $\sigma$ ,  $\alpha$ ,  $\beta$
- 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=ZI8tGWNcKLI](http://www.youtube.com/watch?v=ZI8tGWNcKLI)
- 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, 2<sup>nd</sup> 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 microarray 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](http://www.pmean.com/category/HumanSideStatistics.html)
- [www.pmean.com/category/RandomizationInResearch.html](http://www.pmean.com/category/RandomizationInResearch.html)
- [www.pmean.com/category/SampleSizeJustification.html](http://www.pmean.com/category/SampleSizeJustification.html)
- <http://www.cs.uiowa.edu/~rlenth/Power/>