Issues in Randomization

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Submit your ideas for December 7 lecture!

- Examples due by November 23 (2 weeks; a Monday) to

  johnslau @ mail.nih.gov
- Studies you want used as an example for study development
- Might be from the popular press, a protocol you are working on, from a journal (but I need to be able to research it)

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Objectives: Randomization Lecture

- Identify
  - Reasons and mechanisms for randomization
  - Types of randomized study designs
  - Nonrandomized experimental studies
- Compare randomized experimental studies to nonrandomzied observational studies

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Outline

- **Introductory Statistical Definitions**
- What is Randomization?
- Randomized Study Design
- What is a random sample? A Control?
- Statistical Software

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Vocabulary (1)

- Sample size: N or n
  - May refer to total or per group!
- Mean: average; sum / n
- Median: 50%; middle ordered value
- Variance: σ^2 (population) or s^2 (sample)
- Standard deviation: σ or s
- Standard error: $\sigma/\sqrt{n}$ or $s/\sqrt{n}$

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Vocabulary (2)

- Odds ratio
- Relative risk
- Proportion: ranges 0 to 1
  - For example 45% = 0.45
- A|B is said, “A Given B”
  - P(A|B): “If B is true, what is the probability of A?” or “What is the probability of A given B is true?”

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Vocabulary (3)

- $Y_i = \beta_0 + \beta_1 x_{1i} + \varepsilon_i$
- Y = outcome or response variable
  - Might not be an actual response
- X = covariate, variable
- β_0 = intercept
  - Average value of Y when X = 0
- β_1 = slope, coefficient
- ε = error, residual, difference between sample fit or prediction and person

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$$Y_i = \beta_0 + \beta_1 x_{1i} + \varepsilon_i$$

- Subscript ‘i’ is person *i;* i = 15
  - Y_{15} = 119 (SBP); x_{15} = 1 (on treatment)
- $Y = \beta_0 + \beta_1 x_1$ general sample model
  - Say β_0 = 150, β_1 = -20
- $Y_{15} = \beta_0 + \beta_1 x_{15} + \varepsilon_{15}$
  - Thus $119 = 150 - 20*1 + \varepsilon_{15}$
  - So $\varepsilon_{15} = 119 - 150 + 20 = -11$
  - Difference between Y_{15} and model predicted Y_{15} = -11

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Vocabulary (4)

- Statistic: Compute from sample
- Sampling Distribution
  - All possible values statistic can have
  - Samples of a given size randomly drawn from the same population
- Parameter: Compute from population
  - Usually unknown to researcher
  - Several large studies in population

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Quasi Experimental or Non-Randomized Experimental Studies

- No control group
  - Early in investigation
- Concurrent control "group"
  - Treatment assignment not by randomization
- Historically controlled
  - Missing/poor data
  - Non-comparability of groups

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Randomization: Definition

- Not a random sample
- Random Allocation
  - Known chance receiving a treatment
  - Cannot predict the treatment to be given
- Eliminate Selection Bias
  - Outcome measurements can be biased
- Similar Treatment Groups
  - Does not eliminate baseline differences
  - If baseline differences they arose by chance

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ONE Factor is Different

- Randomization tries to ensure that ONLY ONE factor is different between two or more groups.
  - Chance if 80% women in one group and 20% in the other
- Observe the Consequences
- Attribute Causality

- In truth, a rarity and cannot test

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Ways to Randomize

- Standard ways:
  - Random number tables (see text)
  - Computer programs
  - randomization.com
    - Three randomization plan generators
- NOT legitimate
  - Birth date
  - Last digit of the medical record number
  - Odd/even room number

Who/What to Randomize - Independence

- Person
  - Might take several biopsies/person
- Provider
  - Doctor
  - Nursing station
- Locality
  - School
  - Community

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Should I Randomize? Almost Always YES; But Pitfalls

- Small sample size
- Rare condition
- Rare confounding factors
- People do what they want anyway
  - Testing Life as practiced! (at your local gym, drug or health food store)
  - Wikipedia killed some blinding/masking
- Post randomization exposed non-randomly
  - Medication mix up and control group gets wrong investigational agent

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Types of Randomization

- Simple
- Blocked Randomization
- Stratified Randomization
- Baseline Covariate Adaptive Randomization/Allocation
- Response Adaptive Randomization or Allocation (using interim data)
- Cluster Randomization

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Simple Randomization

- Randomize each patient to a treatment with a known probability
  - Corresponds to flipping a coin
- Could have imbalance in # / group or trends in group assignment
- Could have different distributions of a trait like gender in the two arms

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Block Randomization

- Insure the # of patients assigned to each treatment is not far out of balance
  - Block size = 6, 2 study interventions (A and B)
    - AAABBB, BAABAB, ABABAB….
- Variable block size (permuted)
  - An additional layer of blindness
- Different distributions of a trait like gender in the two arms possible

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Stratified Randomization

- A priori certain factors likely important (e.g. Age, Gender)
- Randomize so different levels of the factor are **BALANCED** between treatment groups
- Cannot evaluate the stratification variable

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Stratified Randomization

- For each subgroup or strata perform a separate block randomization
- Common strata
  - Clinical center, Age, Gender
- Stratification MUST be taken into account in the data analysis!

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Adaptive ?Randomization?
Same Title, Different Meanings

- **Baseline Covariate**
  - Minimization/Dynamic allocation
  - Pocock & Simon (biased coin)
- **Adaptive Randomization/Allocation**
  - Using interim outcome data
  - Play the winner or 2-armed bandit
  - Bayesian

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Baseline Covariate Adaptive Randomization/Allocation

- Minimization/Dynamic Allocation
  - Balance on the margins
    - Table 1 looks pretty
  - Does not promise overall treatment arms balanced in #
- Pocock & Simon (biased coin)
  - Baseline covariates
  - Weighted probability (not 50/50)

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Why not just stratify?

- Typically, many many variables
- Will not have people in each "cell" if do traditional stratification
  - How many participants
    - Pittsburgh Site, Male, 40-64,
    - AND Grade 2, hormone therapy, 6-18 mo post treatment,
    - AND……

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Response Adaptive Randomization/Allocation

- Outcome data during trial (interim)
- Unbalance # / arm in favor of the 'better' treatment(s)
  - Ethically appealing to some
- Difficult to do well
  - Computer programming, not simple
  - All blinded but statistician

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Adaptive Randomization
Difficult

- Programming is not easy
- All blinded but statistician
- Ignore covariates
  - Unknown can lead to problems
  - Treatment-covariate interactions
    - Imbalances may be backwards within subgroups
  - Time trends/drift

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Response Adaptive

- May be group sequential designs
- May use continuous interim analysis to feed into randomization
- May use set interim analysis time points to feed into randomization

- Do not want response to be too long term

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Cluster Randomization

- Same ideas as before
- Unit of randomization
  - School/Clinic/Hospitals
  - Providers
- Outcome measurement
  - Students
  - Patients
- Need to use special models for analysis because those providing outcomes nested in unit that was randomized

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Example

- Try this at home!
  - Or at NIH at the next Thursday evening session
- Bags of hard shell chocolate candy
  - Or other similar candy if you prefer

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Example

- How many bags?
- Different sizes of bags?
- Number of types of candy?
- Number of colors in each?

Randomization Example

- N = 56 (nice R21 size)
- Different types of randomization
- 2 arm study
- 6 colors: red, orange, yellow, blue, green, black

- Compare to N = 20 example

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Simple Randomization

- Perform a simple randomization
- Record the results
- Repeat as long as you have time (3-5 minutes)

Simple Randomization #1

Randomize 56, 3 Times
Simple Randomization

	1	2	3
N/arm	28:28		
Red 9	4:5		
Orange 8	4:4		
Yellow 3	2:1		
Blue 11	5:6		
Green 16	10:6		
Black 9	3:6		

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Simple Randomization #2

Randomize 56, 3 Times
Simple Randomization

	1	2	3
N/arm	28:28	38:18	
Red 9	4:5	6:3	
Orange 8	4:4	7:1	
Yellow 3	2:1	1:2	
Blue 11	5:6	5:6	
Green 16	10:6	10:6	
Black 9	3:6	9:0	

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Randomize 56, 3 Times
Simple Randomization

	1	2	3
N/arm	28:28	38:18	17:39
Red 9	4:5	6:3	2:7
Orange 8	4:4	7:1	4:4
Yellow 3	2:1	1:2	1:2
Blue 11	5:6	5:6	3:8
Green 16	10:6	10:6	4:12
Black 9	3:6	9:0	3:6

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Randomize 20, 5 Times
Simple Randomization

	1	2	3	4	5
N/arm	9:11	9:11	11:9	6:14	14:6
Red 4	2:2	2:2	2:2	0:4	3:1
Orange 5	1:4	2:3	2:3	2:3	4:1
Yellow 4	2:2	2:2	3:1	0:4	2:2
Blue 2	2:0	1:1	1:1	1:1	2:0
Green 3	1:2	1:2	2:1	1:2	2:1
Black 2	1:1	1:1	1:1	2:0	1:1

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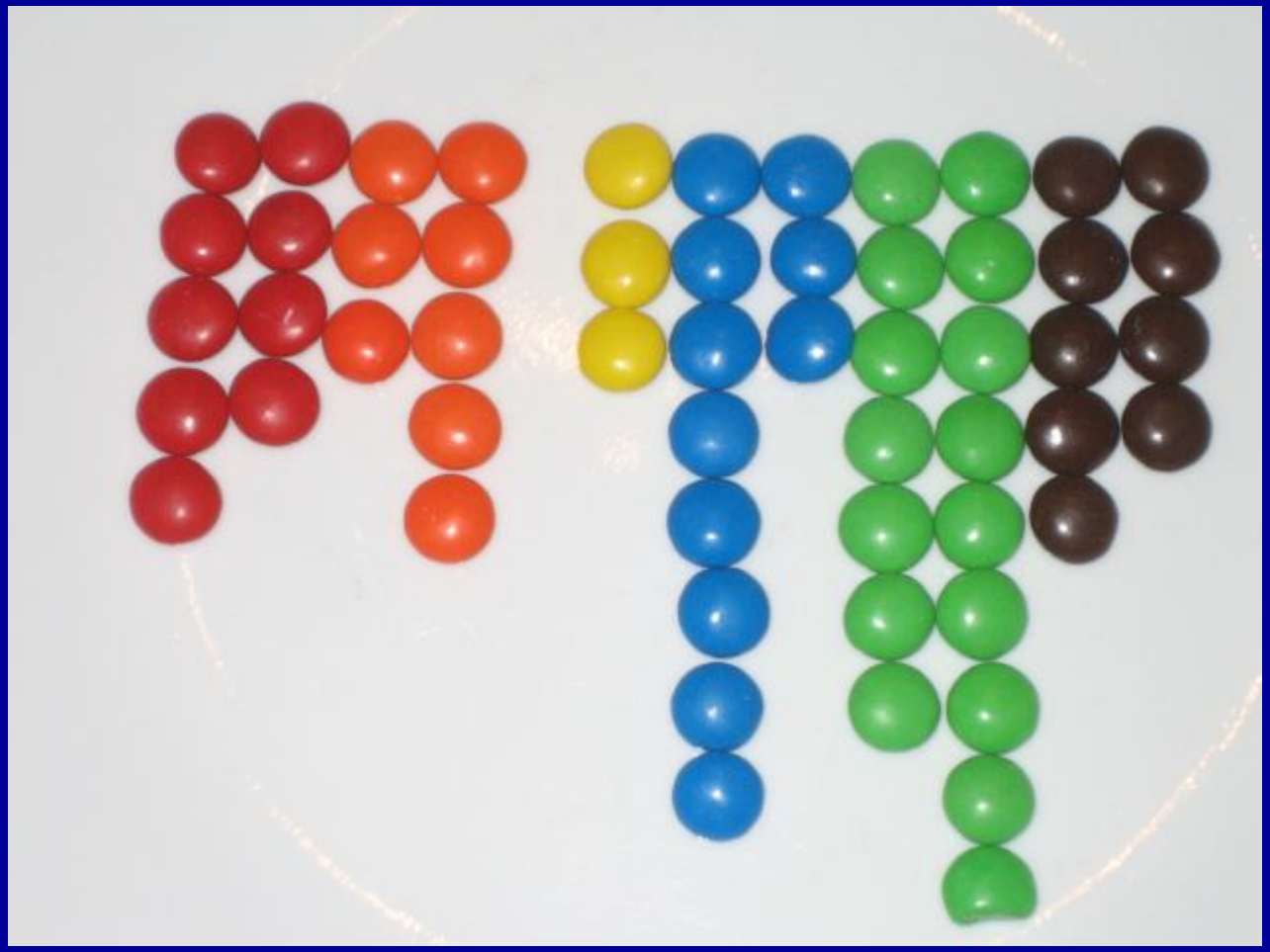
Block Randomization

- Try again
- Use (simple) Block Randomization

Simple Block Randomization



Randomize 56, Blocks

	Block
N/arm	28:28
Red	5:4
Orange	3:5
Yellow	0:3
Blue	8:3
Green	7:9
Black	5:4

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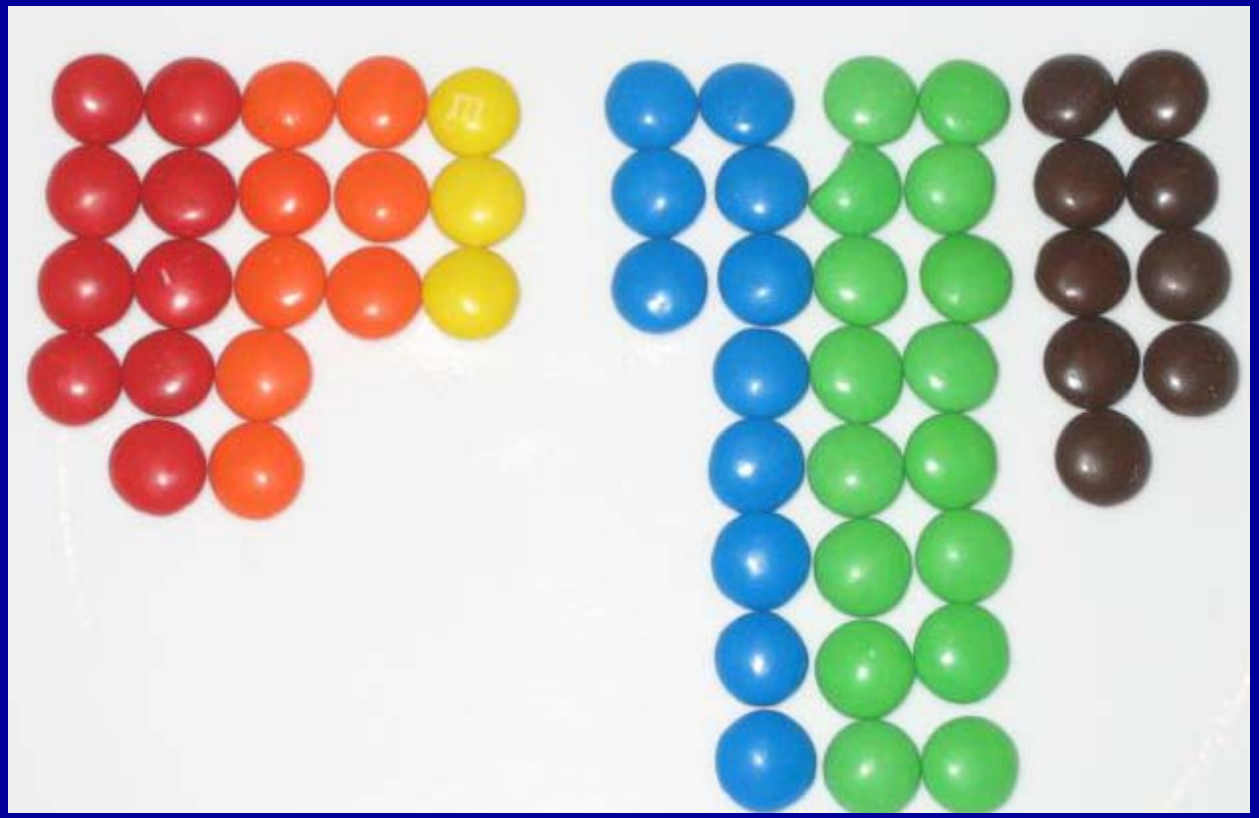
Permuted Block Randomization

Permuted Block Randomization



Randomize 56, Blocks

	Block	Permuted Block
N/arm	28:28	28:28
Red	5:4	4:5
Orange	3:5	5:3
Yellow	0:3	3:0
Blue	8:3	3:8
Green	7:9	8:8
Black	5:4	5:4

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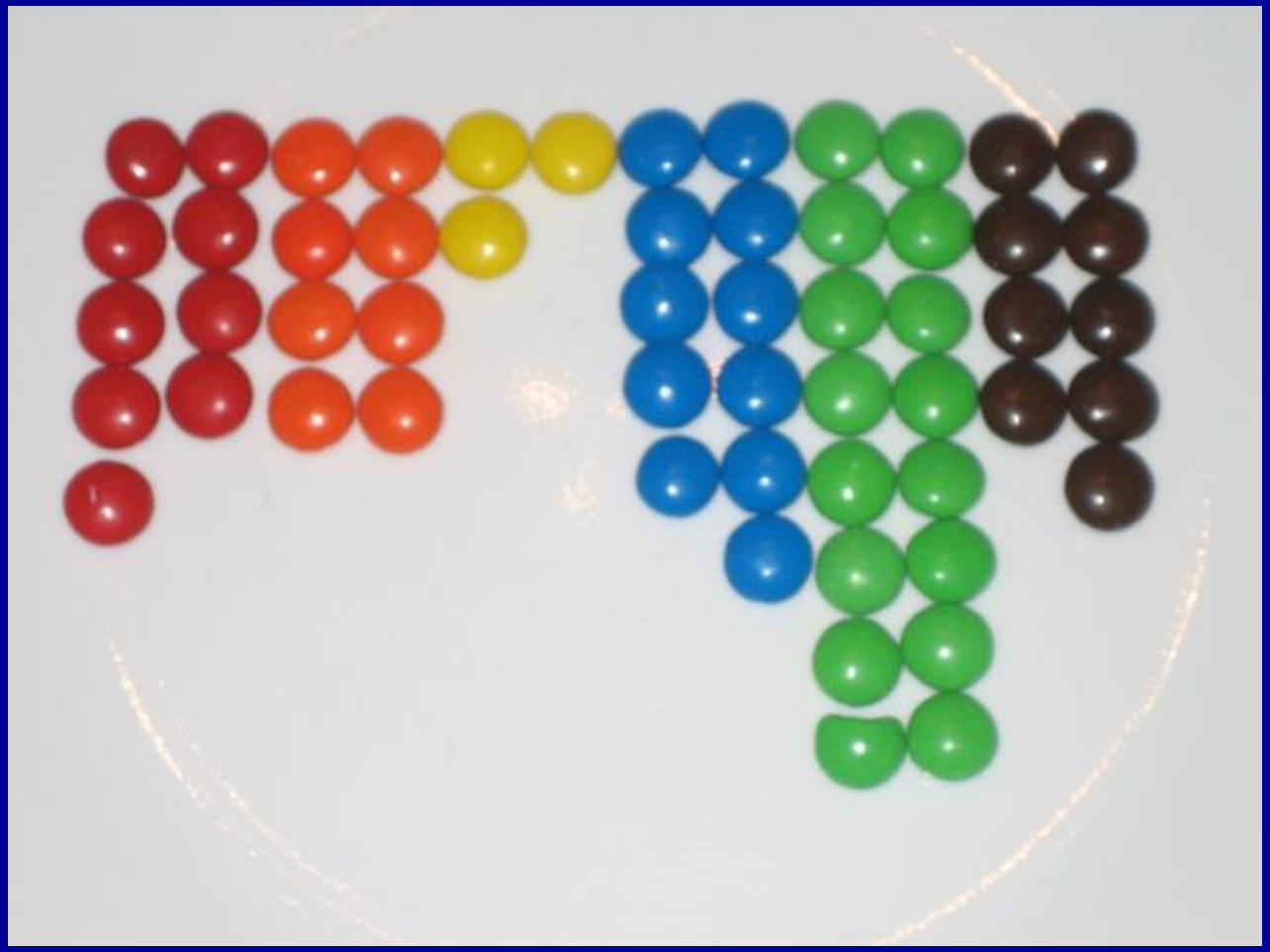
Stratified Permuted Block Randomization

Stratified Permuted Block Randomization



Randomize 56, Blocks

	Block	Permuted Block	Stratified Perm. Bl.
N/arm	28:28	28:28	28:28
Red	5:4	4:5	5:4
Orange	3:5	5:3	4:4
Yellow	0:3	3:0	2:1
Blue	8:3	3:8	5:6
Green	7:9	8:8	8:8
Black	5:4	5:4	4:5

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Randomize 20, Blocks

	Block	Permuted Block	Stratified Perm. Bl.
N/arm	10:10	10:10	10:10
Red	2:2	2:2	2:2
Orange	2:3	2:3	2:3
Yellow	3:1	3:1	2:2
Blue	2:0	1:1	1:1
Green	1:2	1:2	2:1
Black	0:2	1:1	1:1

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Many Ways to Randomize

- Choose one
  - Appropriate to sample size
  - Choose block size(s) appropriate to sample size
- If I have to choose one
  - Permuted block randomization
    - Stratified by site

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Where was the Adaptive Allocation?

- Too much programming for this class, but it could be done
- See a trusted source for details

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Time to Randomize?

- When the treatment must change!
- SWOG: 1 vs. 2 years of CMFVP adjuvant chemotherapy in axillary node-positive and estrogen receptor-negative patients.
  - JCO, Vol 11 No. 9 (Sept), 1993

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Randomize at the Time Trial Arms Diverge

- SWOG randomized at beginning of treatment
- Discontinued treatment before relapse or death
  - 17% on 1 year arm
  - 59% on 2 year arm
  - Main reason was patient refusal

Even if 2 weeks later?

- Long term use of beta blockers post MI
- 393 randomized 2 weeks prior to starting therapy
- 162 patients treated
  - 69 beta blocker
  - 93 placebo

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Randomized, Treated, Analyzed

- 393 randomized
- 162 patients treated
- "…appears to be an effective form of secondary therapy …."
  - Paper reported on analysis of n=162

- What about the 231 randomized but dropped from the analysis?

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Intent to Treat vs. Completers

- ITT = Intent To Treat analysis
  - Assume all study participants
    - Adhered to the study regime assigned
    - Completed the study
- MITT = Modified ITT analysis
  - ITT, but only include people who take the first dosage
- Completers or Adherers analysis
  - Only the well behaved

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Take Home

- Permuted block randomization
  - Stratified by site
  - Appropriate to sample size
  - Choose block size(s) appropriate to sample size
- Randomize smallest independent element at last possible second
- ITT (intent to treat) analysis

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Outline

- ✓Introductory Statistical Definitions
- ✓What is Randomization?
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  - What is a random sample? A control?
  - Stat Software

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Study Design Taxonomy

- Randomized vs. Non-Randomized
- Blinded/Masked or Not
  - Single-blind, Double blind, Unblinded
- Treatment vs. Observational
- Prospective vs. Retrospective
- Longitudinal vs. Cross-sectional

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Ideal Study - Gold Standard

- Randomized
- Double blind / masked
- Treatment
- Prospective
- Parallel groups

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Types of Randomized Studies

- Parallel Group - classic
- Sequential Trials – physical sciences
- Group Sequential trials - classic
- Cross-over – very useful if useable
- Factorial Designs - independence
- Adaptive Designs – gaining popularity

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Parallel Group

- Randomize patients to one of k treatments
- Response
  - Measure at end of study
  - Delta or % change from baseline
  - Repeated measures
  - Function of multiple measures

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Sequential Trials

- Not for a fixed sample size/period
- Terminates when
  - One treatment shows a clear superiority or
  - It is highly unlikely any important difference will be seen
- Special statistical design methods

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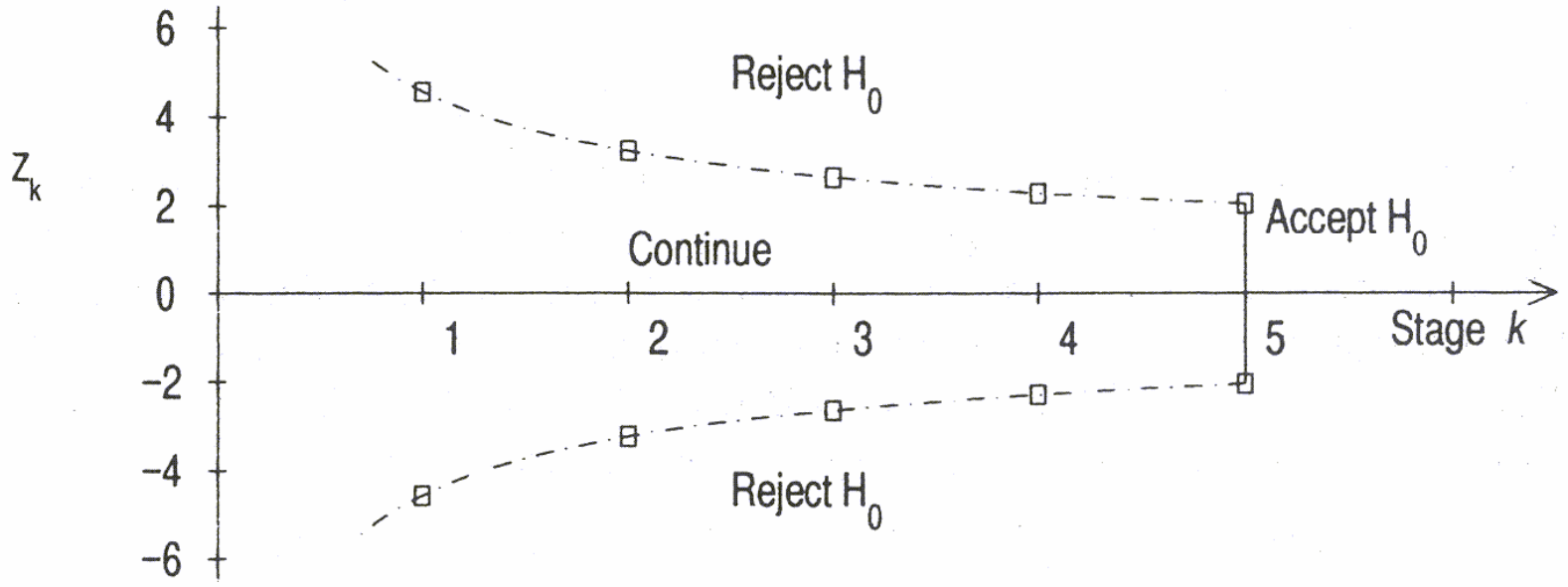
Group Sequential Trials

- Popular
- Analyze data after certain proportions of results available
- Early stopping
  - If one treatment clearly superior
  - Adverse events
- Careful planning and statistical design

Group Sequential Bound Example

Figure 2.2 *An O'Brien & Fleming test for five groups of observations*



Factorial Design

- Each level of a factor (treatment or condition) occurs with every level of every other factor
- Selenomethionine (Se) and Celecoxib (C) Gastroenterology 2002; 122:A71

SE Placebo C Placebo	Selenium C Placebo
SE Placebo Celecoxib	Selenium Celecoxib

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Factorial Design

- Factor 1: Selenium
  - Yes, No
- Factor 2: Celecoxib
  - Yes, No

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Factorial Design

	Se (Placebo)	Se (Real)
Celecoxib (Placebo)	Se Placebo C Placebo	Selenium C Placebo
Celecoxib (Real)	Se Placebo Celecoxib	Selenium Celecoxib

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Factorial Design

	Se (Placebo)	Se (Real)
Celecoxib (Placebo)	Se Placebo C Placebo	Selenium C Placebo
Celecoxib (Real)	Se Placebo Celecoxib	Selenium Celecoxib

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Factorial Design

- Power for the interaction or not?
- Is this a 4 arm study?
- 2-2 arm studies?

SE Placebo C Placebo	Selenium C Placebo
SE Placebo Celecoxib	Selenium Celecoxib

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Incomplete/Partial/Fractional Factorial Trial

- Nutritional Intervention Trial (NIT)
- 4x4 incomplete factorial
- A,B,C,D
- Did not look at all possible interactions
  - Not of interest (at the time)
  - Sample size prohibitive

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Crossover Trial

- E.g. 2 treatments: 2 period crossover
- Use each patient as own control
- Must eliminate carryover effects
  - Need sufficient washout period

Women's Alcohol Study

JNCI 2001

- Three 8-week dietary periods
  - 30g alcohol/day
  - 15g alcohol/day
  - alcohol free placebo beverage
- *Order of assignment* to 3 alcohol levels was random
- Varying washout; double blind

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Adaptive Designs

- Gaining popularity
- 2-8+ arms
- Dose ranging (perhaps)
- Smaller overall sample size (potentially)
- Run-in then analyze data continuously or at fixed points

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Adaptive Designs

- Act like a group sequential design
- Close an arm early
- Re-estimate sample size based on a nuisance parameter (variance)

- Any time a decision to continue is made, information is provided

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Observational

- Can ONLY show Association
- You will never know all the possible confounders!

Randomized

- Can show Association AND Causality
- Well done non-adaptive randomization → unknown confounders should not create problems

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Random Sample vs. Randomization

- Random sample: chance determines who will be IN the sample
- Randomization: chance determines the ASSIGNMENT of treatment

Random Sample

- Draw from the population
- Use a probability device
- Select names out of a hat
  - Now randomize them to treatment assignments
- A few types of sampling to get names into the hat (not randomization)
  - Simple
  - Stratified
  - Cluster

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Simple Random Sample

- Every possible subject chosen from a population for investigation has an equal chance of being selected from the population

- Stop laughing

Stratified Sampling

- Select independent samples
- Number of subpopulations, groups, strata within the population
- Might gain efficiency if done judiciously

Cluster Sampling

- Sample in groups
- Need to look at intra-cluster correlation

Controls

- Really, this is a different topic
- What are we randomizing people to?

What is the control group?

- Placebo
- Most widely accepted treatment
- Standard treatment
- Most accepted prevention intervention
  - Condoms and HIV?
- Usual care
- Accepted means of detection (dx) / diagnostic test

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Control Groups

- Ethical
  - Control intervention itself
  - Assigning ANYONE meeting study criteria to ANY study group
- If "standard of care" (SOC) evidence it really is standard practiced usual care in that format
- Good controls can always be masked?
  - No, sometimes IV versus pill of the same medication
  - Try to mask the interventions, though

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- ✓Randomized Study Design
- ✓Experimental vs. Observational
- ➢Stat Software

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Statistical Resources

- Software
- Books
- Articles
- Colleagues
- Internet

Software

- Most is expensive and some have yearly license fees
  - NIH (through CIT) many times has the software for free or cheaper than retail; CDC and universities do, too
- Some is hard to use, some is easy

Software: Programming Options

- S-PLUS (Windows/UNIX): Strong academic and NIH following; extensible; comprehensive
  - www.insightful.com
- R (Windows/Linux/UNIX/Mac): GNU; similar to S-PLUS
  - www.r-project.org
  - www.bioconductor.org

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S+ and R

- Produce well-designed publication-quality plots
- Code from C,C++, Fortran can be called
- Active user communities

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Other Software

- STATA (Windows/Mac/UNIX)
  - Good for general computation, survival, diagnostic testing
  - Epi friendly
  - GUI/menu and command driven
  - Active user community
  - www.stata.com

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Other Software

- SAS (Windows/UNIX)
  - Command driven
  - Difficult to use, but very good once you know how to use it
  - Many users on the East coast
  - www.sas.com
- SPSS, EpiCure, many others

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Statistical Calculators

- www.randomization.com
- http://calculators.stat.ucla.edu/
  - "Statistical Calculators"
  - Down recently
- http://statpages.org/
- http://www.biostat.wisc.edu/landemets/
- http://www.stat.uiowa.edu/~rlenth/Power

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Questions?