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Study Designs

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Section A

Treatment Allocation Method; Blinding of Assigned Treatment

Allocation History

- Earliest trials used arbitrary methods based on convenience
  - Prior case series
  - Patients treated in different sites
  - Arbitrary division of concurrently appearing points
- More systematic methods in early 20th Century
  - Alternating patients
  - Alphabetical
  - Day of the months
- Randomization  “paradigm shift”

Treatment Allocation

- Allocation variations:
  - Stratified
  - Blocked
  - Group (cluster)
  - Adaptive

Blinding/Masking

- Blinding limits bias
  - Patient response
  - Physician attitude
  - Outcome evaluation
  - Decision-making
- Not all trials can be blinded
  - Distinctive side effect(s)
  - Method of administration
- Grey areas
  - Placebo injections
  - Extra blood draws
  - Sham surgery

Blinding/Masking

- Single blind: patient doesn't know treatment
- Double blind: patient and treating physician
- Triple blind: patient, treating physician and outcomes evaluator
- Unblinded or open label: usually refers to patient and treating physician, can still involve blinded outcome evaluation

Blinding/Masking

- Selection bias
  - Occurs when allocation to one treatment is more likely (predictable)
  - This is why randomization and unpredictability are so important
  - And we need to protect against possible known causes of selection bias and unknown ones

Randomization: Why Do It?

- **To Maintain Trial Integrity**
- Produces study groups comparable with respect to known and unknown risk factors
- Removes possible investigator bias in allocation of participants
- Guarantees that statistical tests will have valid significance

Insoluble Research Problems

- Lack of representative sampling
- Imprecise subject selection
- Non-randomized treatment allocation
- Inclusion of inappropriate controls
- Unblinded subjects/evaluators
- Subjective assessment of outcome

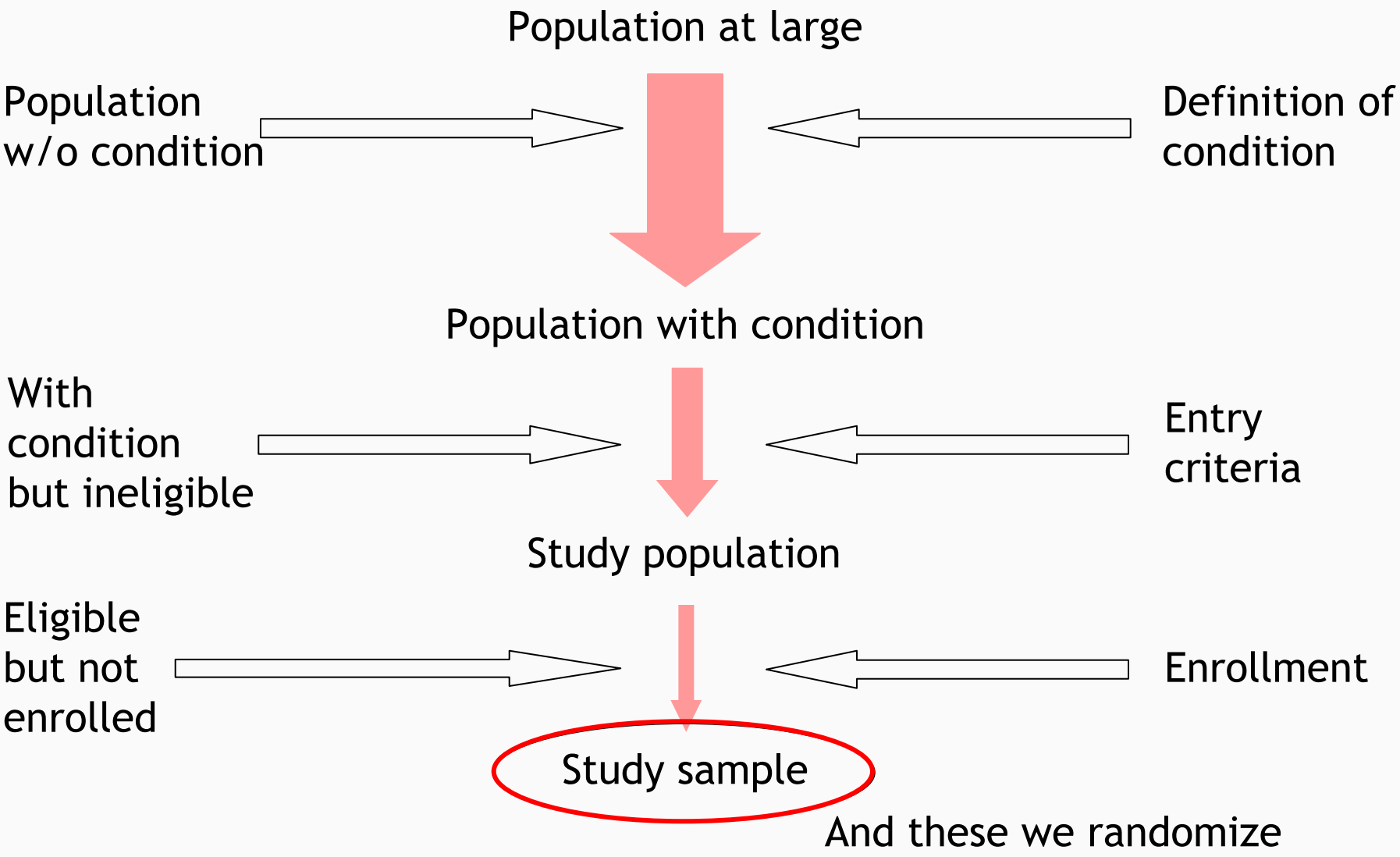
Randomization Principles

- Treatment assignment based on chance alone
  - All subjects are equally likely to be assigned to any group
- Reduces systematic differences
  - Subjects in each group can be expected to possess essentially the same characteristics

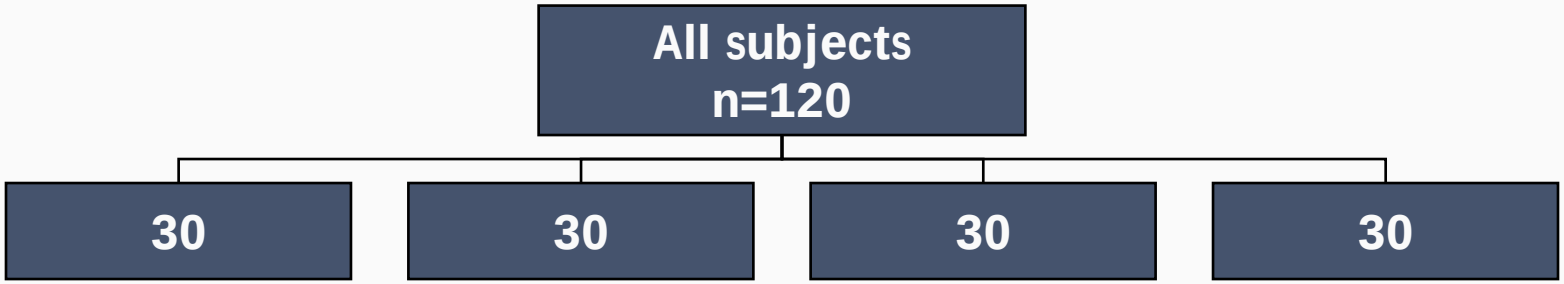
Identical Baseline Characteristics

- The ideal experimental model for comparing two treatments is one in which the baseline characteristics of the two study groups are identical in all aspects

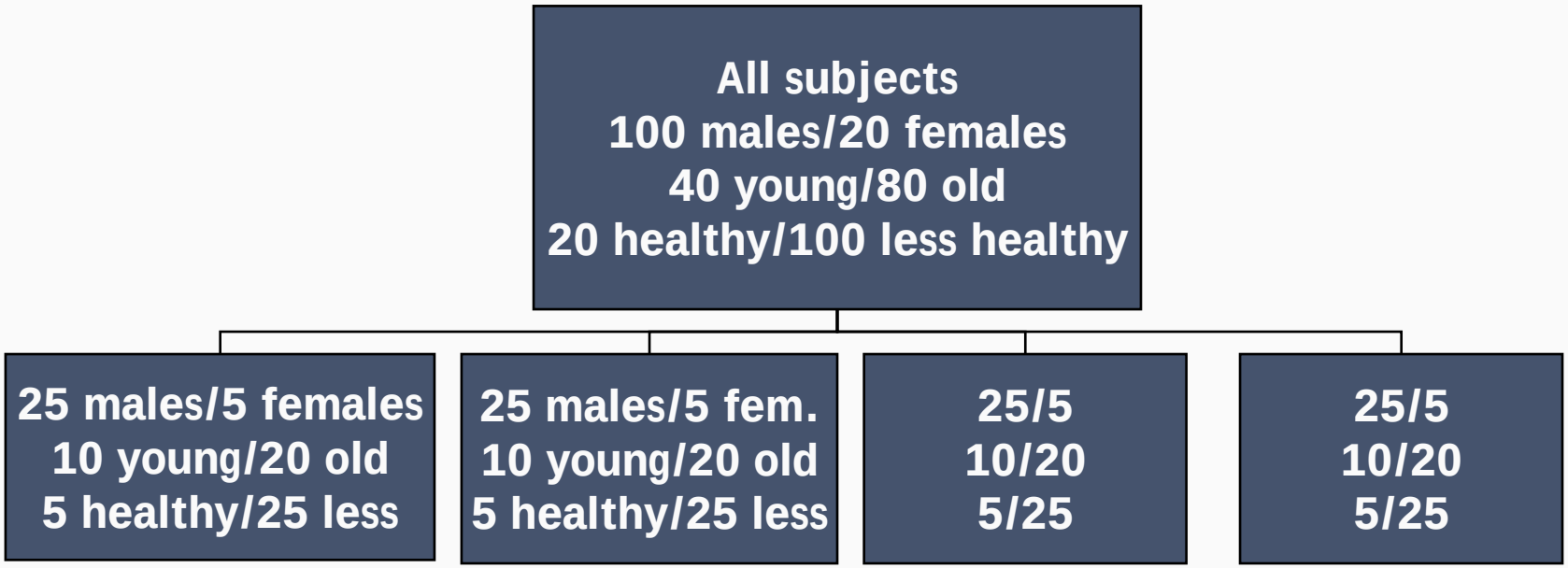
Sample Flowchart



Effect of Randomization: Simple Randomization



Effect of Randomization: Stratified Randomization



Post-Randomization Unknowns

- Differential group:
  - Compliance
  - Drop-out/lost-to-follow-up
  - Adverse events
- Trial sabotage/unblinding
- Other unforeseen issues (different treatment effects!)

Suggestions from CONSORT*

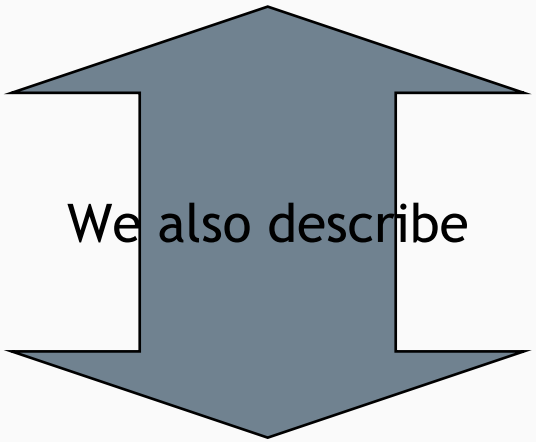
- Assignment/allocation
  - Describe
    - Unit of randomization (person, cluster, etc.)
    - Method used to generate allocation schedule
    - Method of allocation concealment and timing of assignment
    - Method used to separate generator from executor of assignment

Source: Begg, C., et. al. (August 28, 1996). Improving the Quality of Reporting RCTs. *JAMA*. Vol. 276 (8): 637-9
*Note: Consolidation of Standards for Reporting Trials

Random Allocation

- In prospective randomized clinical trials, there is typically a single sample of patients chosen by a non-random set of methods, and THEN random allocation is employed for treatment assignment

- By calling our methods random allocation



- Bias-free treatment assignment

Requirements of Good Allocation Schemes

- Assignment remains masked (“blinded”) to the patient and all study personnel
- Future assignments can not be predicted
- The order of allocations is reproducible
- The generation process has known mathematical properties
- The process provides a clear audit trail

Methods with Problems

- Coin toss
- Odd-even schemes (days, dates, time of day)
- Matched samples
- Stratification
- Patient characteristics (date of birth, social security number, medical record number, etc.)
- Systematic (every nth patient)
- Sealed envelopes with assignment codes

Allocation Management

- Code generation
  - Local (single site)
  - Local (multiple sites)
  - Central coordination (for multiple sites)
  - Location of masterfile and logs

Allocation Management

- Site “location” of codes
  - Clinic envelopes
  - Pharmacy
  - On-site computerized generation
  - On-site data center personnel
  - Telephone or computer link to coordinating centre
- Issues
  - Mechanism for updating enrollment database
  - Maintenance of computer/file security

In the Next Section We'll Look at . . .

- More on treatment allocation
  - Blocking
  - Stratification
  - Adaptive randomization
  - Unequal sample size

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Section B

Stratification

Definitions

- **Stratified/strata:** levels of a risk factor or the categorization of risk factors into different levels
- **Blocks:** size of string desired for balancing patient enrollment among trt groups
- **Permuted:** randomly assorted
- **Permuted block:** randomly assorted blocks of a specific size

Image source: www.sxc.hu

Allocation Schemes

- Fixed
  - Simple
  - Blocked
- Stratified
  - Simple random within strata
  - Permuted block by strata
- Adaptive
  - Baseline adaptive (aka: minimization)
  - Response/outcome (Zelen: play-the-winner)
  - Number (uses a priori group allocation ratios)

Fixed Allocation

- Fixed allocation assigns the intervention to participants with a prescribed probability (usually equal)
- Allocation types
  - Simple allocation
  - Blocked allocation
  - Stratified allocation

Fixed Allocation

- Simple
  - Coin toss
  - Random number table
  - Uniform random number generator
- Problem
  - Imbalance in treatment allocations can occur and vary in severity depending on the overall sample size

Simple Allocations

Possible imbalance in simple randomization with two treatments. This table shows the difference in treatment numbers (or more extreme) liable to occur with probability at least 0.05 or at least 0.01 for various trial sizes.		
	Difference in numbers	
Total number of patients	Probability ≥ 0.05	Probability ≥ 0.01
10	2:8	1:9
20	6:14	4:16
50	18:32	16:34
100	40:60	37:63
200	86:114	82:118
500	228:272	221:279
1,000	469:531	459:541

Fixed Allocation

- Blocked
  - A technique which guarantees that at no time during randomization will the imbalance in patient treatment assignment be large, and that at certain times, the number allocated to each group will be equal
- Translation: choose where to have balance, after every nth enrolled subject (e.g., after every 4th, 6th, 10th)
- This number of patients is then called the block size or blocking factor

Reasons for Blocked Schemes

- Serial or seasonal variation in severity of illness within likely subject pool
- Change in standard of care
  - Radiological (e.g., x-ray/ct vs. MRI)
  - Medical
- Psychological
  - Long-term community enrollments
  - Accumulating outcome information

Blocked Randomization

- Advantage
  - Balance between the number of participants in each study group is guaranteed **during** the course of the trial
- Common disadvantage
  - If trial is not blinded, as the end of the block size is reached, the blocking scheme can often be detected and a certain proportion of randomization assignments will be known

Solution: use variable block sizes
(usually randomly assorted)

Fixed Allocations

- An example of permuted blocks using a block size of four with two treatments, A and B
- The following represents all of the unique ways that four people could be assigned to two treatments such that half of them get assigned to A and the other half to B (i.e., the permutations of the sequence):
  - AABB ABAB ABBA
  - BBAA BABA BAAB

Fixed Allocation Problem

- AAB**B** ABAB ABBA
- Problem: if study personnel detect the size of the block (four), they will always know what the last person in a block will receive (e.g., if AAB_ from AABB sequence has already been assigned, it is obvious the next person would receive B)
- Solution: randomize the size of the subsequent block after each current block is used; from the above, after using the first block of four, the next block size could be randomly selected from sized two, four, or eight

Stratification Notes

1. Although simple randomization within strata can be used, blocked randomization is preferred for balance
2. In multi-center trials, the center itself is generally used as one of the stratification variables
3. Controversy remains regarding the need for intra-center stratification on potential risk factors
   - Generally can be handled analytically
   - Design issues and power must be carefully considered
   - All must be pre-specified

Adaptive Randomization

- A technique by which subjects are assigned to a group in a manner that will tend to correct an existing imbalance or cause the least imbalance in prognostic factors
- Types
  - Baseline
  - Response/outcome
    - These techniques can utilize either deterministic or probabilistic schemes

Adaptive Randomization

- The next patient can be assigned not in a completely random way, but such that whichever group they are assigned to minimizes the overall difference between the groups (i.e., makes them as similar as possible)
- Not technically difficult
- Practically can be very difficult!
- If you do not use a computerized algorithm to make such assignments, for some of these schemes you will get completely lost and reproducibility would be impossible to claim

Special Procedure

- Minimization: special case of general adaptive randomization where allocation procedure is **deterministic**
  - **This means that no chance (randomness) is involved**
  - The next patient in a series will simply receive an assignment based on the allocation which reduces any existing imbalance among the groups
  - If no imbalance exists at a given point of assignment, then only that particular patient is randomly allocated

Example (Pocock, 1983)

Factor	Level	Number on each treatment		Next patient
		A	*B*	
Performance status	Ambulatory	30	31	←
	Non-ambulatory	10	9	
Age	<50	18	17	←
	≥50	22	23	
Disease-free interval	<2 years	31	32	
	≥2 years	9	8	←
Dominant metastatic	Visceral	19	21	←
Lesion	Osseous	8	7	
	Soft tissue	13	12	

Example (Pocock, 1983)

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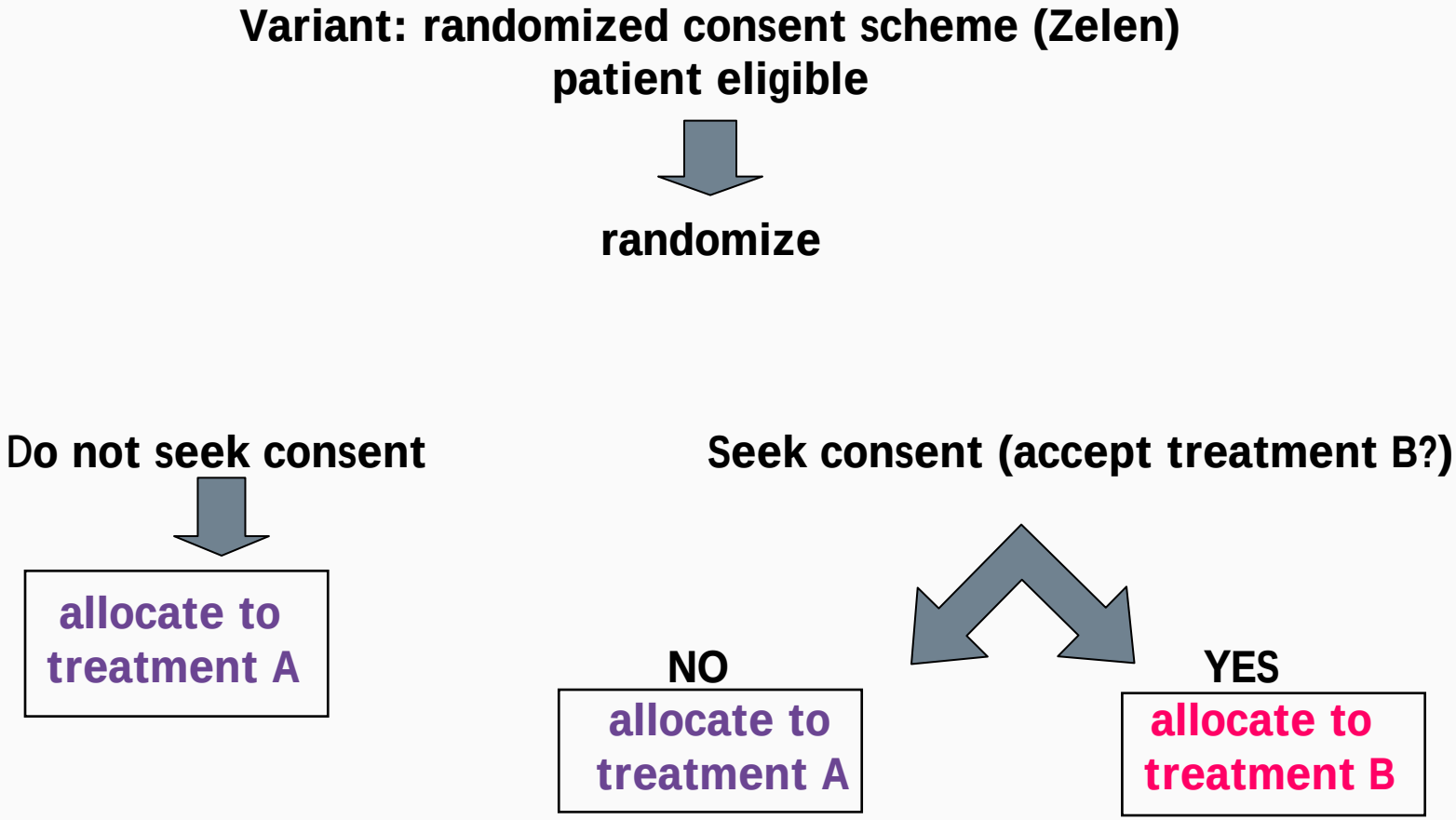
Lesion	Osseous	8	7	
	Soft tissue	13	12	
Totals		76	77	

Other Randomization Issues

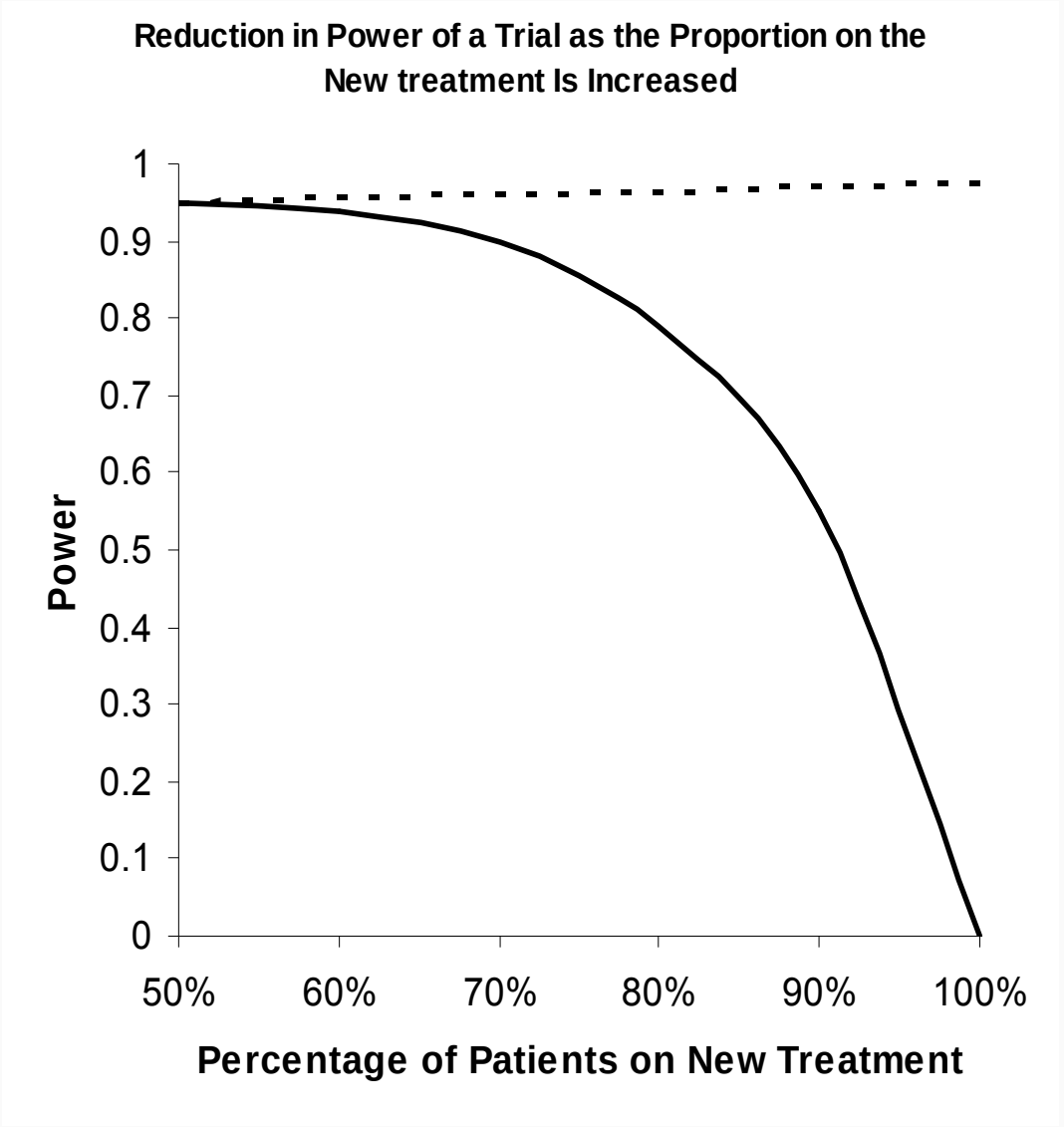
- Important to consider the timing of randomization relative to the start of treatment; this must always be obvious in protocol



Source: Zelen

Statistical Efficiency of Treatment Comparisons

- Statistical efficiency of treatment comparisons when a 1:1 randomization scheme is not used
- Recommendation: if possible, always use 1:1 allocation, but if necessary for assessment of new, standard treatments, use ratio less extreme than 3:1



Source: Pocock, S. (1983). Clinical Trials.

Questions

- How do you decide what to do in your study?
- Should the allocation ration be 1:1 (i.e., 50/50) or some other ratio?
- What about if you have a manufacturing problem?

In the Next Lecture We'll Look at . . .

- Control groups
  - Reasons
  - Types of control
  - No treatment-control, placebo control, active control
  - Historical controls
  - Concurrent controls