

### **Randomization**

patients are assigned to treatment groups by a random mechanism not controlled by the patient or investigator  
increases the likelihood treatment groups have similar distributions of measurable and unmeasurable baseline characteristics

### **Randomization Schedule**

before the study begins, a statistician generates a randomization schedule  
neither the participant nor investigator should know in advance which treatment will be assigned to reduce observation bias  
allocation should be carried out using a chance mechanism and be easy to implement

### **Randomization Ratio**

A = new treatment  
B = control

#### Equal Allocation

1:1 randomization  
patients have a 50% chance of receiving A and 50% chance of receiving B

#### Unequal Allocation

x:1 randomization  
patients have a  $\frac{x}{x+1}$  chance of receiving A and  $\frac{1}{x+1}$  chance of receiving B  
used to detect rare side effects in treatment group

### **Unrestricted Randomization**

assign each treatment randomly and independently of previous treatment assignments  
equivalent to tossing a coin for each subject that enters the trial  
simple, unpredictable, easy to implement treatment assignments  
can produce imbalanced group assignments for small sample sizes, which decreases efficacy

### **Block Randomization**

sequence of blocks that contain the treatment assignment in the desired ratios,  
e.g. randomly permute letters ABAB for the each block to ensure that for every 4 patients, 2 receive each treatment  
in case extra patients need to be randomized, provide a randomization schedule containing more patients than expected  
block size must be a multiple of the numbers in the allocation ratio  
with small block sizes, clinician may be able to guess the pattern  
large block size may lead to incomplete blocks at the end of the schedule  
no one except the statistician needs to know the randomization schedule

### Random Block-Size Randomization

prevent investigator from deducing the block size over time  
choose two block sizes and randomly assign size to each block  
within each block, randomize patients to treatment using permuted block method

### **Stratified Randomization**

stratify randomization by other variables, e.g. center, diagnosis, age group  
generate a separate randomization schedule for each stratum  
too many small strata will cause imbalances in randomization that cancel out the intended beneficial effects of blocking  
use a limited number of strata  
use regression adjustments later if there are imbalances in some baseline factors

### **Adaptive Randomization**

array of methods to determine treatment assignment aimed at making trials more efficient  
adapt the study design using data accumulated from earlier stages of the trial  
requires fewer patients  
randomization lists can't be made before the study

### Minimization

use if number of strata is large  
the first k patients are randomly assigned to treatment groups A or B  
for each subsequent patient, calculate an imbalance score resulting from 2 hypothetical treatment assignments A and B  
deterministic approach = assign patient to the treatment allocation with lower score  
probabilistic approach = give higher assignment probability to treatment with lower score

### Previous Outcomes

as data accumulates, give higher assignment probability to the more effective treatment  
proceed over time until there's enough evidence to make a decision

### **Cluster Randomization**

randomize centers, physicians, or communities rather than individual patients  
make service implementation or treatment delivery easier  
used when there's potential for aspects of intervention to be adopted by placebo group

### **Bias**

selection bias = investigator uses knowledge of upcoming treatment assignment to help decide who to enroll  
observer bias = knowledge of treatment allocation affects the evaluation of the response to treatment  
perception bias

### **Blinding**

process of hiding the treatment a patient receives from the patient, physicians, and/or study personnel  
eliminates potential biases

	<b>Physician</b>	<b>Patient</b>
Double-Blind	blind	blind
Single-Blind	unblind	blind
Open-Label	unblind	unblind

in single-blind and open-label trials, have another physician unaware of treatment allocation  
evaluate the patient for efficacy/safety outcomes  
everyone involved in the conduct or analysis should be blinded