**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 chance of receiving A and 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 permutate 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 ach 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

|  |  |  |
| --- | --- | --- |
|  | **Physician** | **Patient** |
| 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