Clinical and Translational Science Institute / CTSI

at the University of California, San Francisco

Introduction to Randomized Blinded Trials

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OBJECTIVES

1. Explain the rationale for choosing a randomized blinded trial
2. Describe various types of randomized trial designs
3. Describe how to choose the intervention and control
4. Identify how to select study participants
5. Discuss importance of and approach to blinding

Vitamin D and Strength in the Elderly

- Muscle strength and renal function decline with aging
- Declining renal function results in low levels of 1,25 D
- Vitamin D Deficiency causes myopathy and treatment improves strength

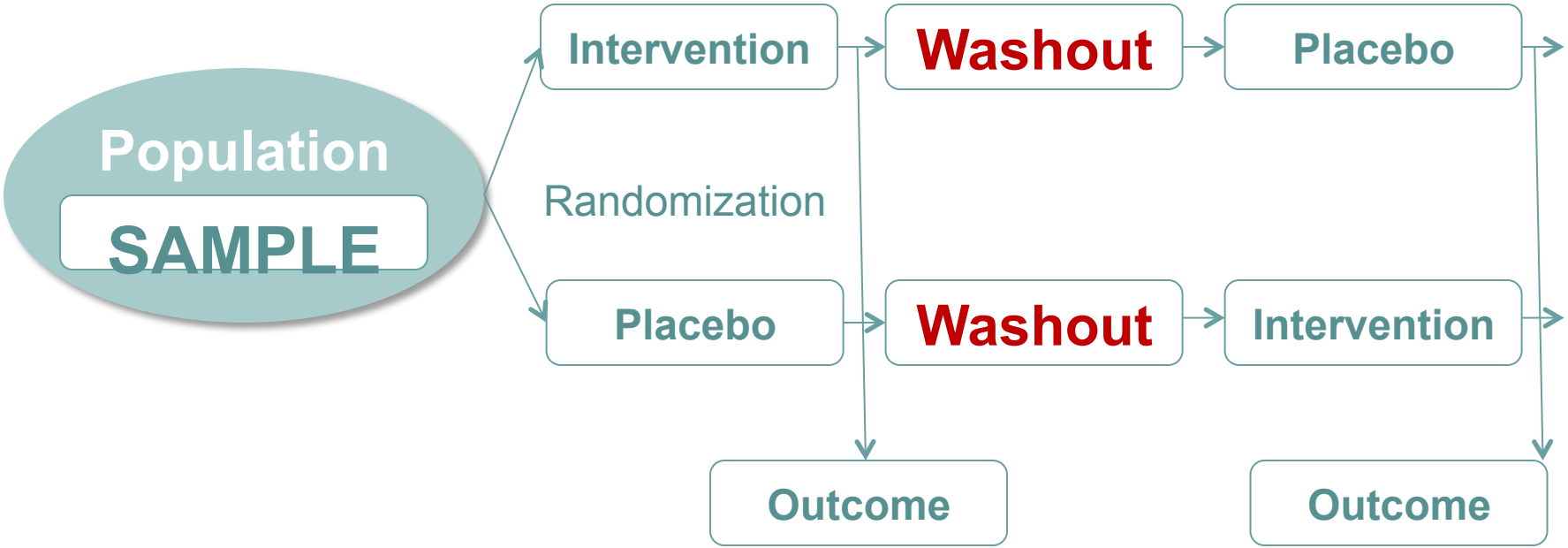
RQ: Does treatment with vitamin D improve strength in the elderly?

Vitamin D and Strength in the Elderly

Basic Trial Design

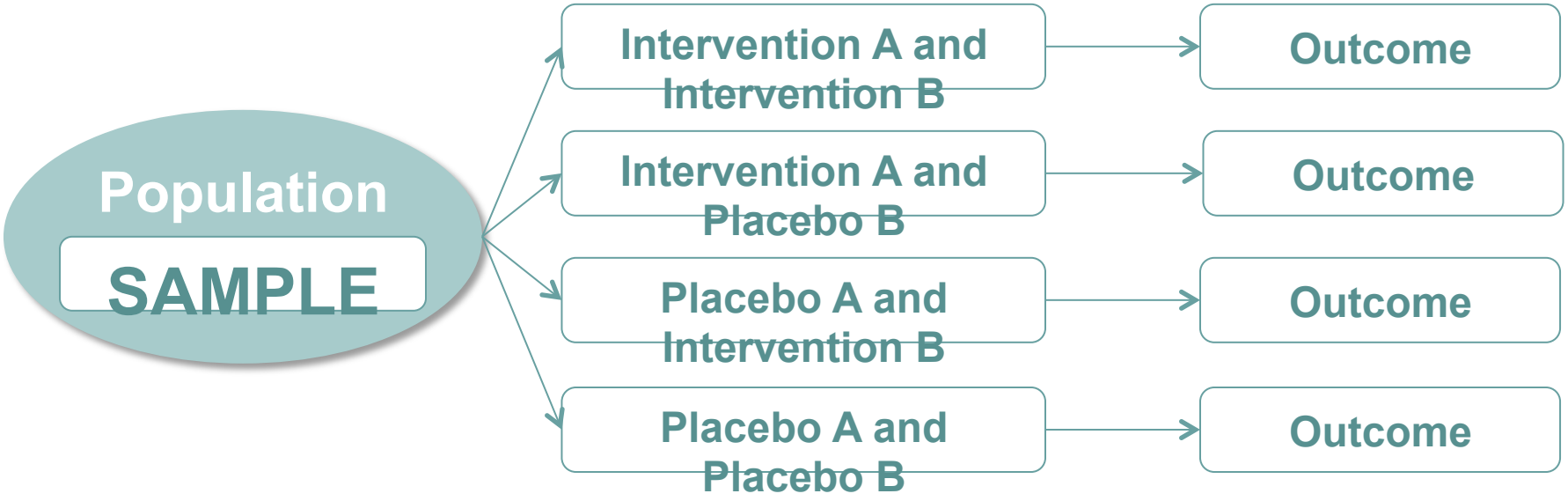
Vitamin D and Strength in the Elderly

Cross-Over Design



Vitamin D and Strength in the Elderly

Factorial Design



Vitamin D and Strength in the Elderly
Randomization

- Participants are assigned to treatment groups by chance with a known probability
- Random number table or computer
- Tamper-proof system
  - Ordered, sealed envelopes
  - Centralized system (phone, fax, web)

Value of Randomization

- Balances baseline characteristics of the treatment groups
  - Eliminates confounding due to measured and unmeasured factors
  - Provides an unbiased comparison between groups
- Does **NOT** maintain balance after randomization

Variations of Randomization

Fixed Allocation

- Probability fixed
- Simple – flip a coin
- Blocked – randomize consecutive small batches
- Stratified – separate randomization in strata
- Clustered – randomize groups

Adaptive

- Probability changes
- N in the groups (biased coin)
- Baseline characteristics
- Outcome *(play the winner; two-armed bandit)*

Vitamin D and Strength in the Elderly – *Selecting the Intervention*

Maximize:

- efficacy *(highest tolerable dose)*
- safety *(lowest effective dose)*
- generalizability
- trial design / conduct
  - *recruitment*
  - *compliance*
  - *blinding*

Vitamin D & Strength in the Elderly

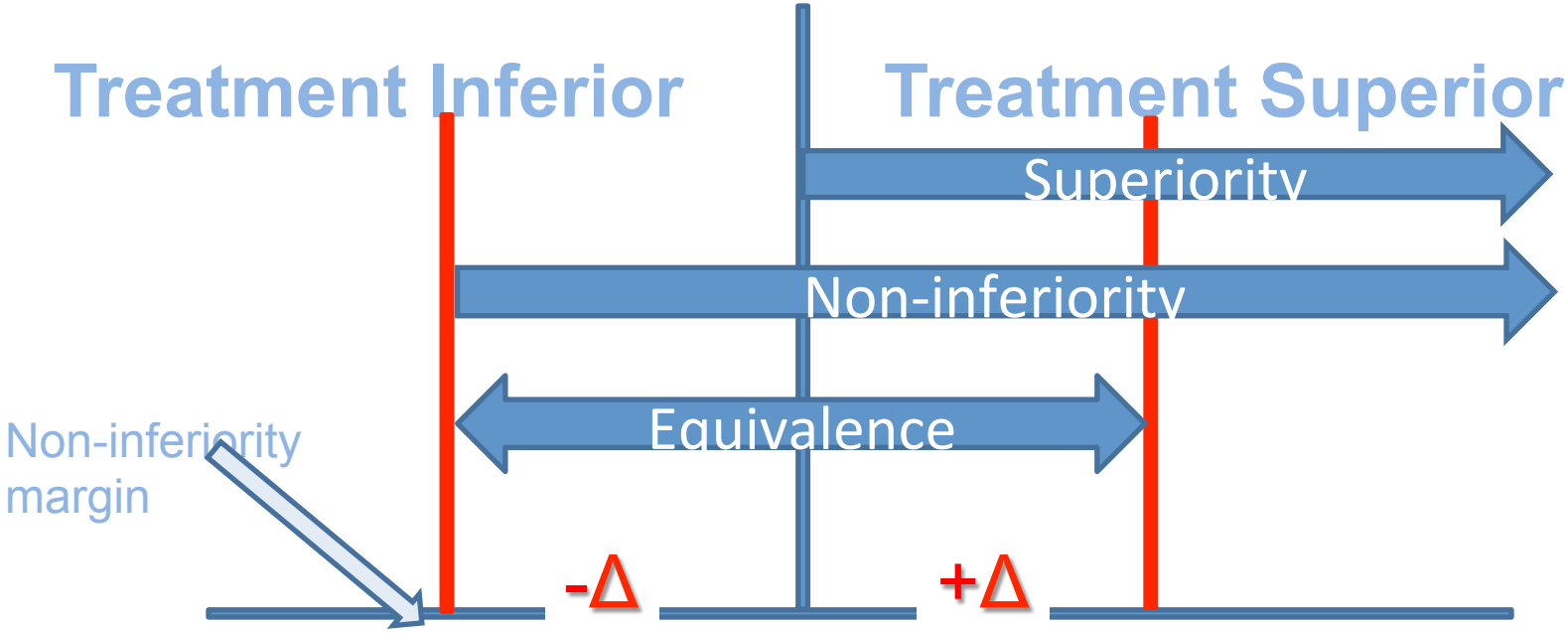
Choice of Control

- Inert placebo usually best
- Active therapy or “standard of care”
  - Active Comparator Trial
  - Superiority Trial– new therapy more effective than standard
    - *Ho: two treatments equally effective*
    - *Ha: one treatment more effective*

Equivalence and Noninferiority Trials

- Use this design if a new treatment has advantages in ease of use, lower cost, or tolerability over established treatment (*e.g.* less side effects, better delivery system)
- Use confidence interval to design these trials, proving no difference between groups=infinite sample size
- Select a delta Δ to create non-inferiority margin

Equivalence and Non-Inferiority Trials



Treatment-Control

Equivalence and Non-inferiority Trials

Advantages

- Better answer to clinical question
- Might be more ethical

Disadvantages

- Requires larger sample size
- Negative result may be due to poorly conducted trial
- Can't tell if either better than placebo

Only reasonable if good standard of care and potential advantage of new therapy

Vitamin D and Strength in the Elderly – *Participants*

Inclusion criteria:

- Rate of outcomes (old, weak)
- Likely benefit from intervention (renal dz, institutionalized, low vitamin D)
- Generalizability
- Ease of recruitment

Vitamin D & Strength in the Elderly

Participants

Exclusion criteria:

- Intervention unsafe
- Intervention unlikely to be effective
- Participant unlikely to adhere to the intervention
- Participant unlikely to complete follow-up
- Practical problems

Practice Parsimony

Preserve Generalizability

Vitamin D & Strength in the Elderly

Considerations

- ***Dose*** – in renal insufficiency 0.25 – 1.0 ug SQ 1,25 daily normalizes calcium
- ***Duration*** – few months usually restores strength in patients with rickets and myopathy
- ***Route*** – SQ vs PO?
- ***Titration*** to normal 1,25-D level or normal (safe) urine calcium?

Why Blind?

- Maintains balanced groups during follow-up
- Eliminates
  - Co-intervention
  - Biased outcome ascertainment
  - Biased measurement of outcome

Physicians' Health Study

- 22,071 male physicians
- Aspirin 325mg QOD or placebo
- Follow-up 5 years
- Outcomes – CVD events and death
- Many physicians had study drug tested for ASA

Cointerventions

- Unintended effective interventions
  - ***Participants*** use other therapy or change behavior
  - ***Study staff, medical providers, family, or friends*** treat participants differently
- Nondifferential – decreases power
- Differential – causes bias

Oral Contraceptive Pills to Prevent Pregnancy

- 18,000 women age 21-35 years
- Randomly assigned to OCPs or usual birth control method
- Followed Q6 months for 2 years
- Pregnancy risk decreased 75%
- VTE risk increased 5-fold

Biased Outcome Ascertainment

- If group assignment is known
  - ***Participants*** may report symptoms or outcomes differently
  - ***Physicians or investigators*** may elicit symptoms or outcomes differently

Canadian Cooperative MS Trial

- 165 patients with multiple sclerosis
  - Plasma exchange + cyclo + pred
  - Sham plasma exchange + placebo meds
- Outcome = structured neurologic exam by blinded and unblinded neurologists
- More improvement with plasma exchange by unblinded, but not blinded assessment

Noseworthy, Neurology, 1994

Conclusions

- Randomized trials provide gold standard evidence for treatment efficacy
- Randomization and blinding preserve integrity of trial design
- Consider hypothesis and select trial design to match study goals

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