SUPERIORITY VS. EQUIVALENCE TRIALS

EQUIVALENCE TRIALS

intended to determine that the new treatment is no worse than the active control (the reverse of superiority trials)

- we can never assess absolute equivalence
- we can only assess no difference within a prescribed margin (up to debate)

NULL: the difference between treatments is greater than "X"

ALTERNATIVE: the difference between treatments is less than "X"

POTENTIAL BIAS: incomplete follow-up, low compliance, co-interventions tend to bias results away from the null / toward the alternative: no difference between the groups

SUPERIORITY TRIALS

intended to determine if a new treatment is different from (or better than) placebo or existing treatment (active control)

NULL: there is no difference between treatments

ALTERNATIVE: the new treatment is different from (two-sided) or better than (one-sided) placebo or active control

POTENTIAL BIAS: incomplete follow-up, low compliance, co-interventions tend to bias results toward the null

Why do equivalence trial?

- existing effective treatments available
- Placebo-controlled trial would be unethical (e.g. life-threatening illness)
- New treatment is not substantially better than the existing treatment
  - may have fewer side effects, greater convenience, lower cost, higher quality of life, or provide an alternative or second-line therapy option

Bias in Equivalence Trials

- **Incomplete follow-up and Low compliance:** may limit observed response and therefore bias results toward no difference
- **Co-interventions:** may create 'ceiling' in response and therefore bias results toward no difference
- **Measurement error:** increases variability and the size of the confidence interval; increases the likelihood of inconclusive results
- **Un-blinding:** may bias results in an unknown direction; blinding particularly important in equivalence trials

Challenges in Equivalence Trial Design:

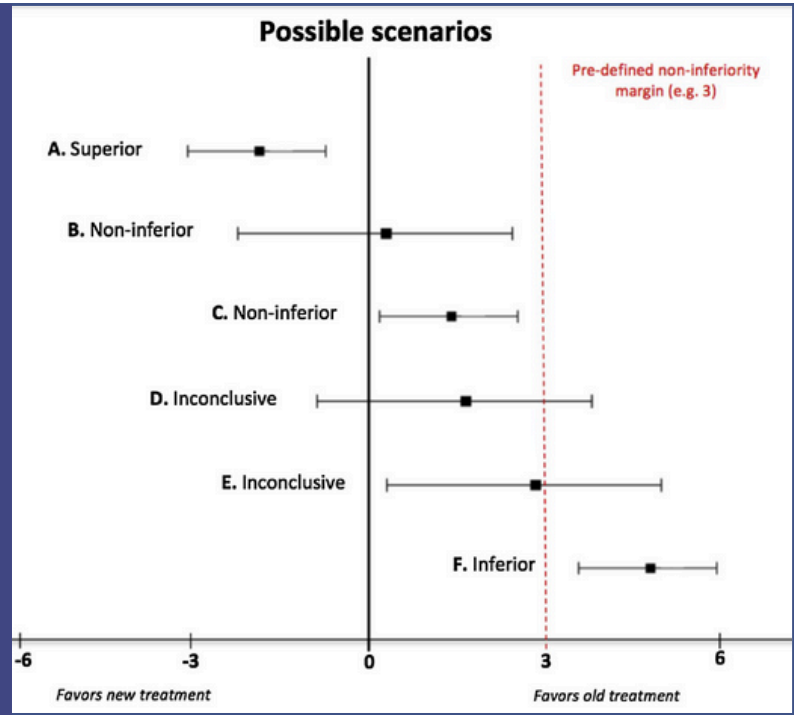
- changing the cutoff from clinically "significant" to "insignificant" often leads to a 50% reduction int he size of the confidence intervals
  - this can increase the sample size 4 times
- Necessity of a gold standard for existing therapy (active control)
  - may not exist if multiple treatments exist
- Necessity to establish equipotent doses of new treatment and active control
  - requires prior testing of multiple doses of each drug
  - difficult to know if smaller prior study has not been conducted
- Best condition for new therapy may not match previous research for active control
  - testing of new therapy as a second line treatment

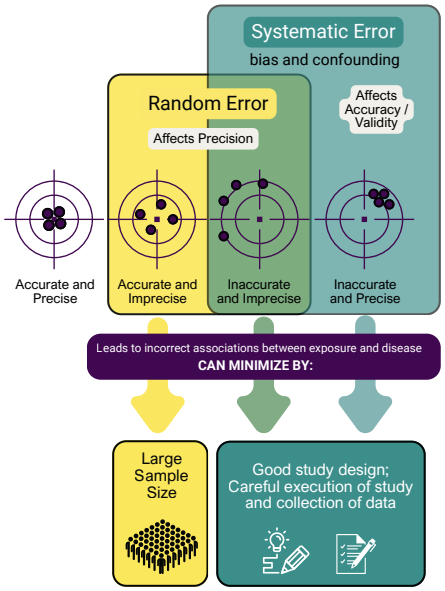
Interpreting the Equivalence Margin

- if confidence interval lies **entirely within** the equivalence margin, then it's considered **"equivalent"**
- if confidence interval lies **entirely outside** the margin, then one drug is determined as **"superior"**
- if confidence interval **crosse the margin**, then results are considered **"inconclusive"**

How to set the equivalence margin:

- superiority trials set sample size to detect a "clinically significant" difference
- Equivalence trials set sampl size to establish "clinically insignificant" difference
- "Clinically insignificant" is determined by information outside of the trial
  - May be a source of grea controversy: has a large impact on sample size





3 PRINCIPLES FOR CASE-CONTROL STUDIES

DECONFOUNDING PRINCIPLE:

MOA should NOT be distorted by confounding, unmeasured confounders should be minimized in the study design (e.g. stratification, matching)

RESTRICTION

MATCHING

OVERMATCHING
Bias toward Null

COMPARABLE ACCURACY PRINCIPLE:

the degree of accuracy in measuring the exposure of interest for the cases should be equivalent to the degree of accuracy for the controls

Nondifferential Misclassification

STUDY BASE PRINCIPLE

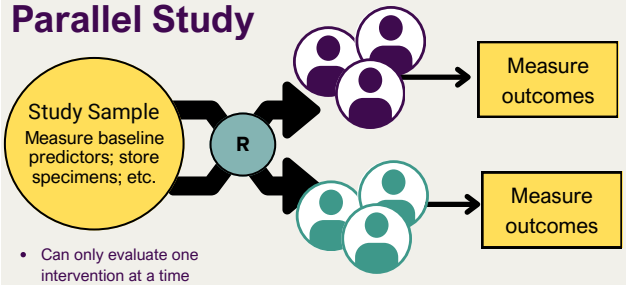
Controls must be selected from the study base that gave rise to the cases. Controls should represent the exposure experience in the study base

CASES

"WOULD CRITERION"

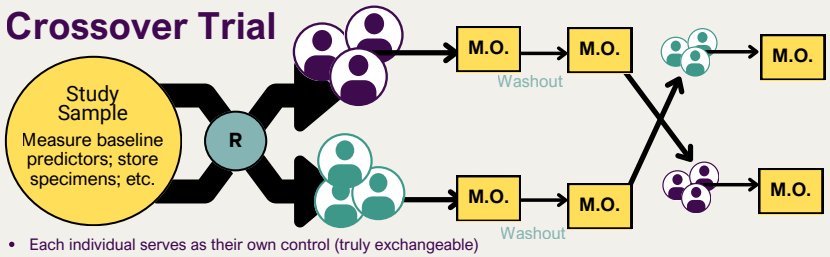
CONTROLS
Would have been identified as a case over the study period if they had acquired the disease

Parallel Study



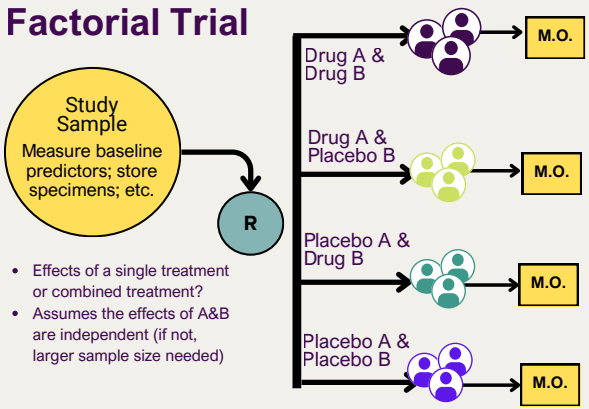
- Can only evaluate one intervention at a time
- Not appropriate for groups

Crossover Trial



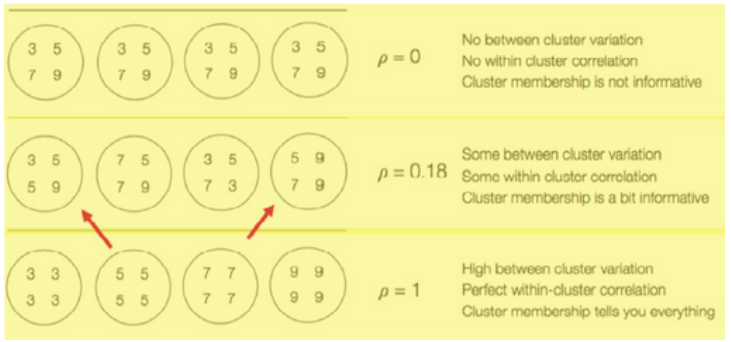
- Each individual serves as their own control (truly exchangeable)
- Carry over effects may bias results toward null
- Interventions need to have short-term effect
- Usually used for chronic or repeated outcomes
- Period effects may bias (changes in disease over time like seasonal flu)

Factorial Trial



- Effects of a single treatment or combined treatment?
- Assumes the effects of A&B are independent (if not, larger sample size needed)

Design	Control Source	OR Estimates:
Risk-Set / Density / Nested Case-Control	Person-time at approximate time when cases occur during follow-up	Incidence density ratio
Case-Cohort	Total cohort at baseline	Cumulative incidence ratio
Cumulative	Total non-disease cohort at time of study	Odds ratio



Categorization of RCT	Trial Types
The aspects of the interventions they evaluate	Efficacy; Effectiveness; Phase 1, 2, and 3
How the participants are exposed to the intervention(s)	Parallel; Crossover; Factorial
The number of participants	From N-1 to Mega; Fixed size; Sequential
Whether investigators and participants can be blinded	Open; Single blind; Double blind; Triple and quadruple blind
Whether preferences of non-randomized individuals are taken into account	Zelen's design; Comprehensive Cohort Design; Wennberg's design
New designs	Double randomized ; Adaptive randomized