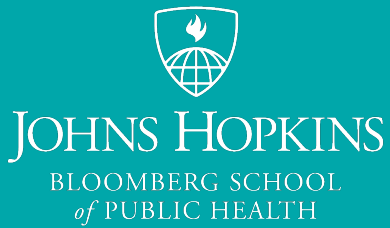


Section B

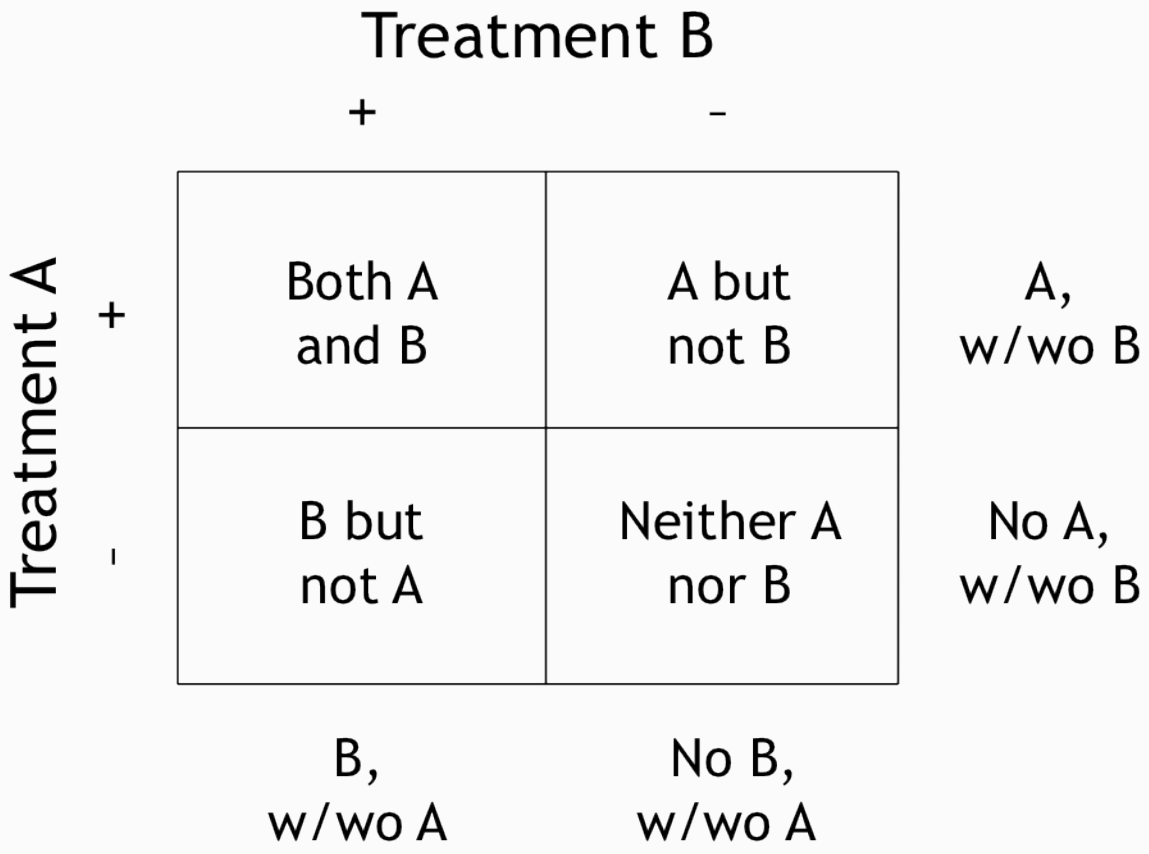
Extensions of the Parallel Design: Factorial and Large Simple Designs

Factorial Design

- Two interventions tested simultaneously, either as . . .
  1. Economical way to test two treatments simultaneously, or
  2. Method to test for treatment interaction

- For testing two treatments simultaneously, assumption is of no interaction
  - Treatments have independent mode of action
  - More plausible if different outcome

Factorial Design Graph

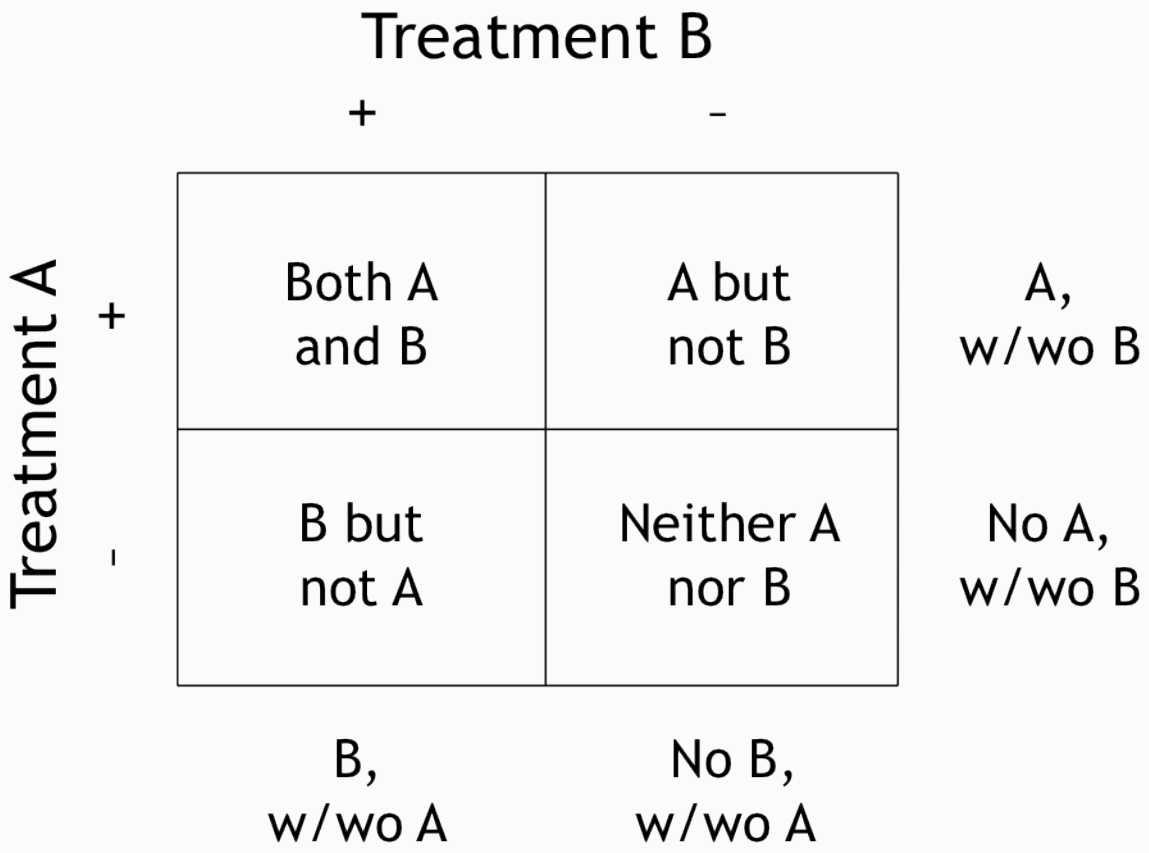


Factorial Design: Comparisons

- Estimation of main effects, if no interaction expected
  - Use numbers in the margins
    - A vs. no A, regardless of assignment to B
    - B vs. no B, regardless of assignment to A
  - Determine response

- Assessment for interaction
  - Is response in A and no A different among those receiving B or no B?
  - May have limited power to detect interaction

Factorial Design Graph



Factorial Design Example: ISIS-3

- International Study of Infarct Survival–3
- Factorial design: 3 x 2
  - Aspirin + heparin vs. aspirin alone (antithrombotic)
  - Streptokinase vs. tPA vs. APSAC (fibrinolytic)
- Large, simple trial
- 41,299 patients
- 914 hospitals
- 20 countries

ISIS-3 Treatments

SK + Aspirin plus heparin (6,893 patients)	tPA + Aspirin plus heparin (6,870 patients)	APSAC + Aspirin plus heparin (6,893 patients)	Subtotal 1: 20,656 patients allocated aspirin plus heparin
SK + Aspirin alone (6,887 patients)	tPA + Aspirin alone (6,876 patients)	APSAC + Aspirin alone (6,880 patients)	Subtotal 2: 20,643 patients allocated aspirin alone
Subtotal A: 13,780 patients allocated SK	Subtotal B: 13,746 patients allocated tPA	Subtotal C: 13,773 patients allocated APSAC	Total: 41,299 patients

Source: ISIS-3 Collaborative Group (1992). *Lancet 339*: 753-770.

Large, Simple Design

- Features
  - Very large number of patients (many study sites)
  - Broad eligibility criteria
  - Minimal data collection requirements

- Rationale
  - Modest benefits require large sample sizes
  - Treatment interactions unlikely, so baseline characteristics and interim response variables are not needed
  - Less precision (more error, increased variance) is tolerated; countered with large numbers

Large, Simple Design: Requirements

- Easily administered intervention
  - Short-term adherence
  - No treatment adjustment
  - No ongoing monitoring for adverse events
- Easily ascertained outcome
- Short-term follow-up?
- No complex baseline measurements
- Simple data are persuasive enough

ISIS-3 Methods

- No baseline form, randomization by phone call
- Treatment conveniently packaged
- Use of ancillary treatment not restricted
- One-page form at discharge for in-hospital events
- Follow-up for mortality only, used government records when possible

Source: ISIS-3 Collaborative Group (1992). *Lancet 339*: 753-770.