Types of Trial Design

Lea Drye, PhD
Johns Hopkins University

Phases of trials

- Phase I:
  - First stage in testing a new intervention in humans
  - Usually 10-30 people
  - Identify tolerable dose, provide information on drug metabolism, excretion, and toxicity
  - Often not controlled

- Phase II:
  - Usually 30-100 people
  - Preliminary information on efficacy, additional information on safety and side effects

- Phase III:
  - Usually 100+ people
  - Assess efficacy and safety
  - Controlled, usually randomized

Lecture Outline

- Discuss various trial design types
  - Parallel
  - Crossover
  - Group allocation
  - Factorial
  - Large simple
  - Equivalency
  - Non-inferiority
  - Adaptive

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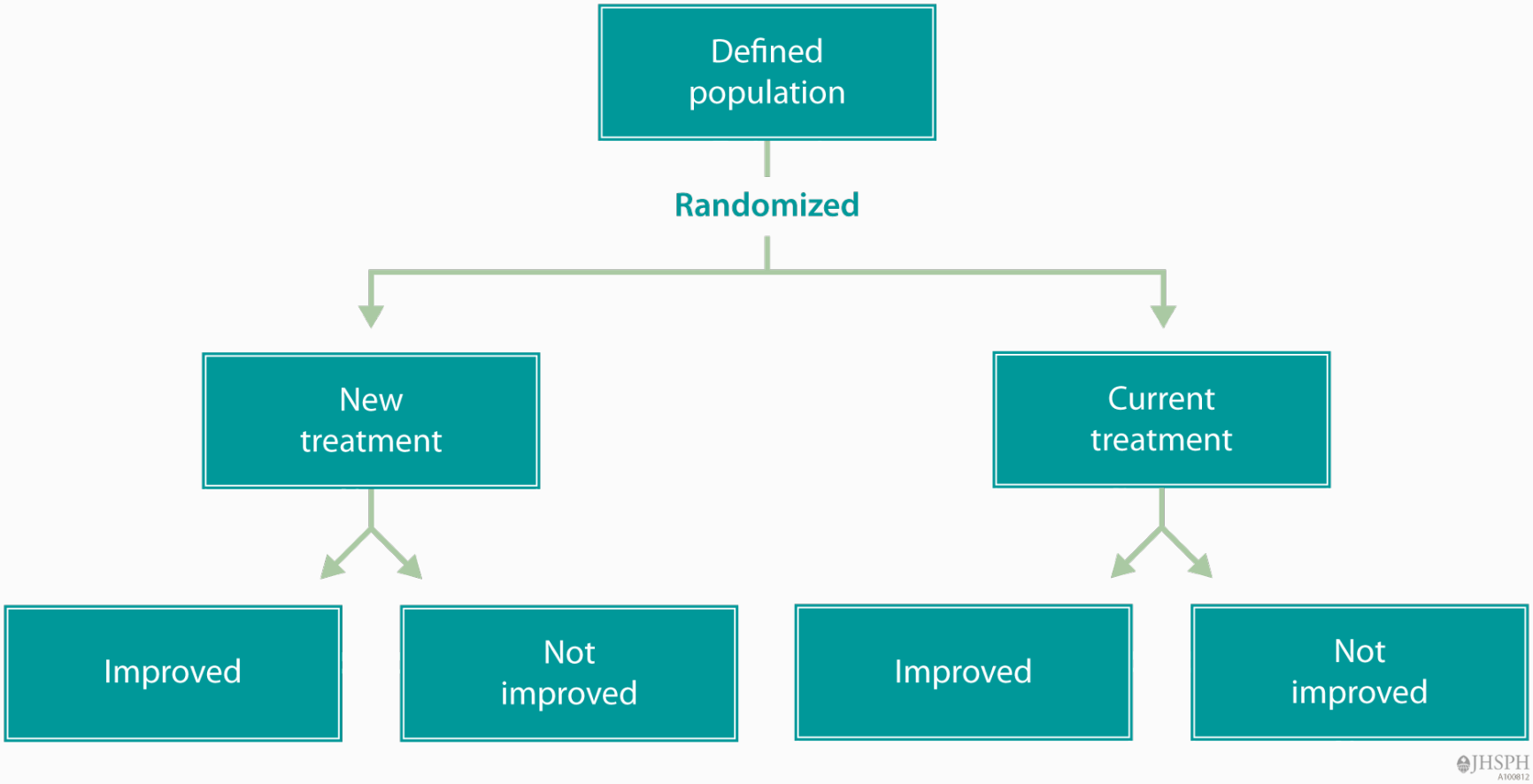
Section A

Comparison Structure: Parallel, Crossover, and Group Allocation Designs

Parallel Design

- Simultaneous treatment and control groups
- Each person is randomly assigned to one treatment group
- Randomization removes treatment selection bias and promotes comparability of treatment groups
- Statistical comparisons made between treatment groups

Parallel Design Graph



Parallel Design Example: NETT

- National Emphysema Treatment Trial (NETT)
  - Phase III trial, unmasked

Population	People with severe emphysema
Sample size	1,200
Allocation to treatment	Randomized
Treatments	—Lung volume reduction surgery plus medical therapy —Medical therapy (standard therapy control)

Source: NETT Research Group (1999). *Chest 1999*; 116: 1750-61; NETT Research Group (1999). *J Thorac Cardiovasc Surg*, 118: 518-528; Fishman, A., & Martinez, F., et al. (2003). *N Engl J Med* 348: 2059-73.

Parallel Design Example: NETT

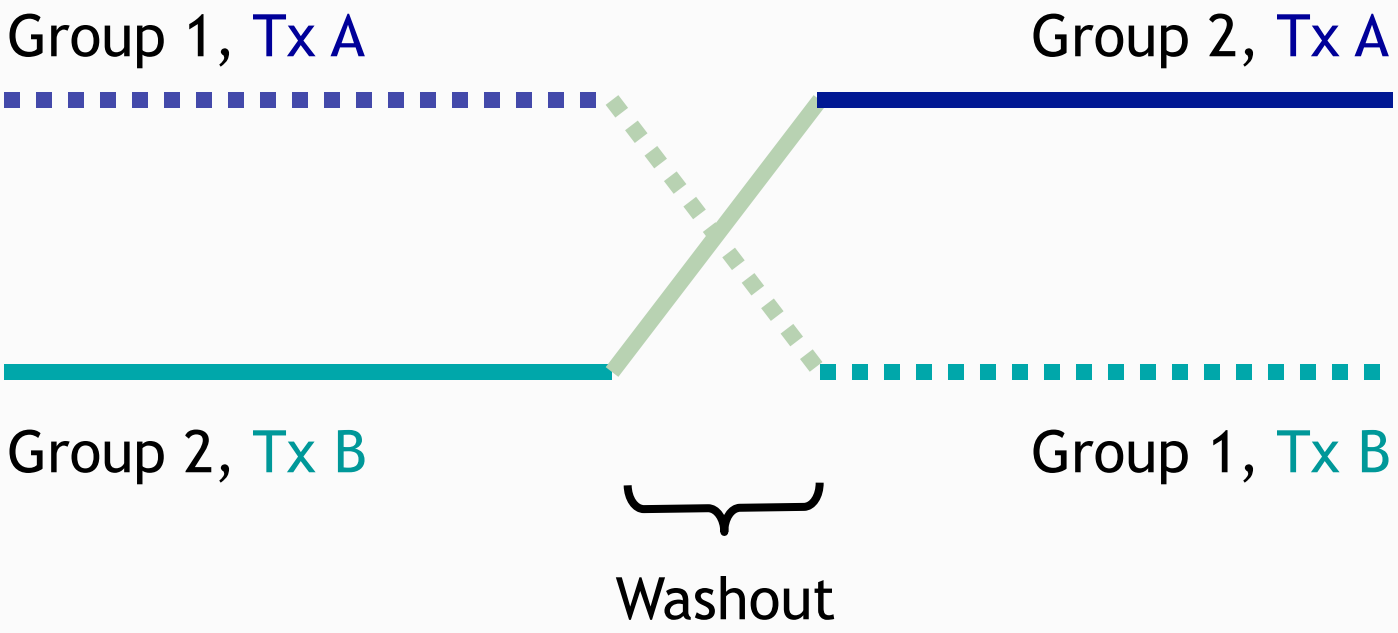
Hypothesis testing	Superiority
Outcomes	—Primary: mortality, exercise capacity —Secondary: quality of life, symptoms, lung function and mechanics, functional capacity
Follow-up	Up to 7.5 years
Number of recruiting centers	Multi-center (17)

Source: NETT Research Group (1999). *Chest 1999*; 116: 1750-61; NETT Research Group (1999). *J Thorac Cardiovasc Surg,* 118: 518-528; Fishman, A., & Martinez, F., et al. (2003). *N Engl J Med* 348: 2059-73.

Crossover Design

- Randomization of order in which treatments are received
  - AB or BA
  - Randomization promotes balance between treatment groups in timing of exposure
- Testing of both treatments in each patient
  - Each patient serves as his/her own control
  - Variability reduced because less variability within patient than between patients
- Fewer patients needed

Crossover Design Graph



Crossover Design: Disadvantages

- Treatment can't have permanent effects or cures
- Potential carry-over effects of first-period treatment to second period
  - Washout needs to be long enough
  - Unequal carry-over effects
  - Treatment during washout
- Test for period by treatment interactions not powerful
- Dropouts more significant
- Analysis may be more difficult

Crossover Design: Uses

- Constant intensity of underlying disease
  - Chronic diseases—asthma, hypertension, arthritis
- Short-term treatment effects
  - Relief of signs or symptoms of disease
- Metabolic, bioavailability, or tolerability studies

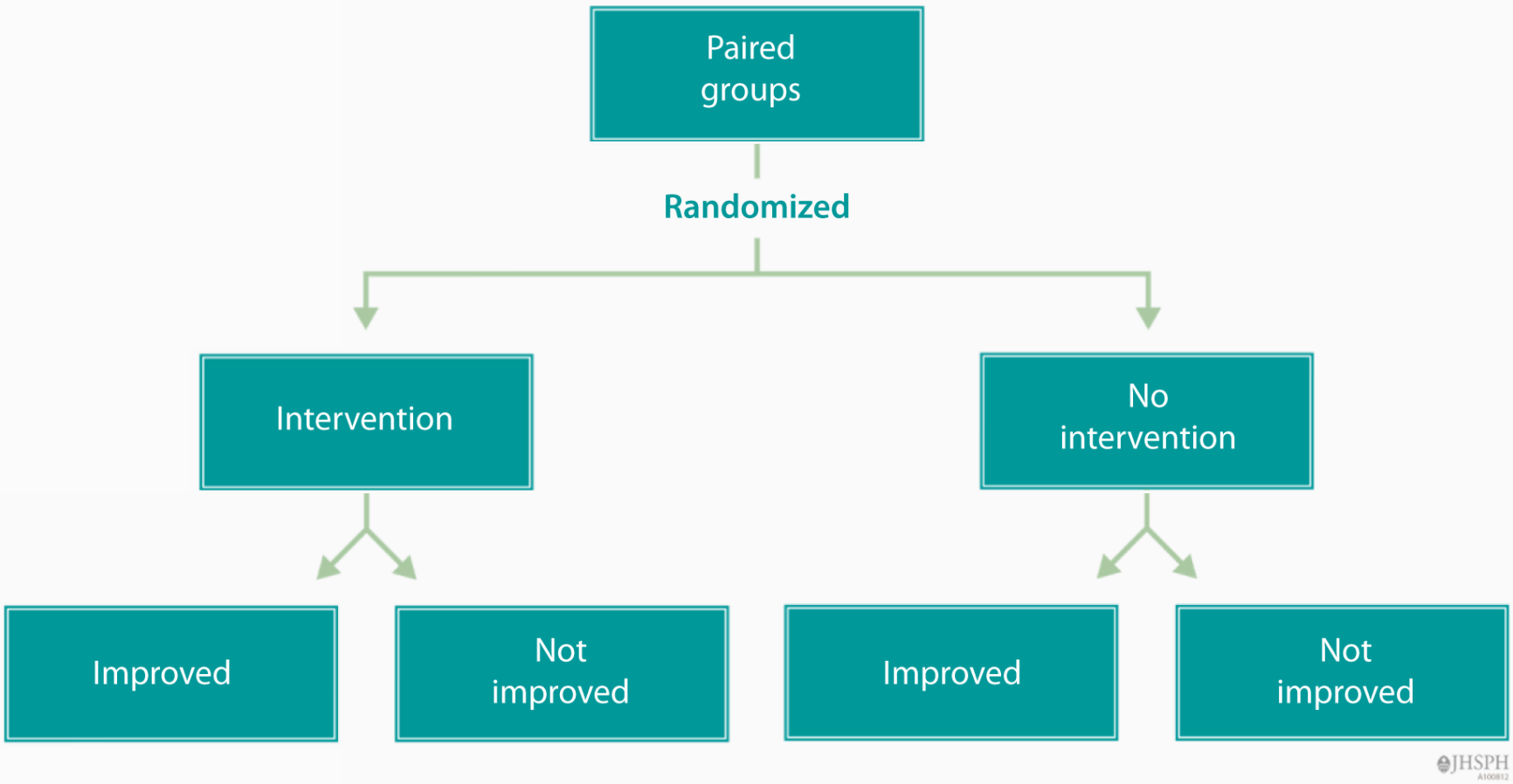
Crossover Design: Examples

- Evening-dose vs. morning-dosed travoprost in open-angle glaucoma for 24-hour intraocular pressure control
- Montelukast vs. salmeterol as adjuvant to inhaled fluticasone for exercise-induced asthma in children
- Topical oil vs. placebo for neuropathic pain

Group Allocation Design

- Also known as “cluster randomization”
- Randomization unit is a group of individuals (community, school, clinic)
- Individual randomization and intervention is not feasible or is unacceptable
  - Tracking
  - Contamination
- If there is a correlation in the responses within a group, design loses some efficiency (more individuals required)

Group Allocation Design Graph



Group Allocation Example: Sommer Vit A trial

- Population
  - Preschool children in northern Sumatra in 1982-83
- Treatments
  - Vitamin A supplementation during study
  - Vitamin A supplementation after study
- Clusters
  - Villages (450) selected using survey sampling method
  - Each randomly allocated to one treatment

Lancet. 1986 May 24;1(8491):1169-73